# RESPIRATORY FLUCTUATIONS OF OXYGEN PRESSURE IN ALVEOLAR GAS AND BLOOD OF THE DOG

HAYATO YOKOTA

PROMOTOR

PROF. DR. F. J. A. KREUZER

# RESPIRATORY FLUCTUATIONS OF OXYGEN PRESSURE IN ALVEOLAR GAS AND BLOOD OF THE DOG

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
IN DE GENEESKUNDE
AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN,
OP GEZAG VAN DE RECTOR MAGNIFICUS PROF. MR. F. J. F. M. DUYNSTEE
VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN
IN HET OPENBAAR TE VERDEDIGEN
OP VRIJDAG 29 JUNI 1973, TE 14.00 UUR PRECIES

DOOR

HAYATO YOKOTA

GEBOREN TE TOKYO, JAPAN

NIJMEGEN 1973
DRUKKERIJ GEBR. JANSSEN B.V.

*This investigation was carried out in the Department of Physiology, University of Nijmegen, under the supervision of Prof. F. Kreuzer. The author is indebted to the partial support of Stichting Voor Medisch Wetenschappelijk Onderzoek FUNGO.*

*The help of the members of the Department of Physiology is deeply acknowledged, particularly of the gas laboratory (chief: Miss B. E. M. Ringnalda), of Mr. W. G. T. v. d. Ven, Mr. L. Frings, and Mr. J. A. M. Evers during experiments, of Mr. J. Michels in preparation of parts of the flowmeter, and of Mr. C. M. Lammerts and Mr. M. J. G. Visser in preparation of oxygen electrodes. Thanks are due to Drs. L. J. C. Hoofd for development of mathematical analysis and preparation of computer program, Dr. R. A. Binkhorst and Drs. L. H. D. J. Booij for translation of a part of the text into Dutch. The author expresses his appreciation to the department of Medical Photography (director: Mr. A. T. A. Reynen) and to the Animal Laboratory (director: Dr. M. J. Dobbelaar) for the supply of experimental animals.*

*To*
*my father*
*Itsuko.*

# *Contents*

Alveolar gas is important because pulmonary gas exchange occurs between it and the blood. However, its composition has been a challenge to physiologists in spite of much progress concerning the underlying mechanisms. In view of the difficulty of obtaining a direct representative sample Zuntz (quoted by Krogh and Lindhard, 1914) for the first time used an indirect method, Bohr's equation, to calculate alveolar gas with the knowledge of the volume of anatomical dead space. Haldane and Priestley (1905), on the other hand, adopted a direct method to obtain alveolar gas, taking the arithmetic mean of two samples of a forced deep expirate at the end of inspiration and expiration. This method, however, was criticized by Krogh and Lindhard (1913, 1914) as giving too high $CO_2$ and too low $O_2$, particularly in exercise; these authors (1914) tried to get a true mean alveolar $O_2$ and $CO_2$ by constructing the time course of alveolar gas variation during the respiratory cycle from several spot samples of the expirate, but their time course of alveolar gas therefore was limited to the expiratory phase. For the assessment of the inspiratory phase of the time course of alveolar gases nearly 40 years had to elapse until Chilton and Stacy (1952) and DuBois *et al.* (1952) reported the moment-to-moment variation of alveolar $P_{CO_2}$ from theoretical consideration and empirical reasoning, showing that the effective alveolar space for $CO_2$ and $O_2$ had to be considered differently. The time course of alveolar $P_{O_2}$ was elucidated by Chilton *et al.* (1954).

Thereafter Yamamoto (1960) calculated the variation of alveolar $P_{CO_2}$ ($P_{ACO_2}$) in his studies of the regulation of ventilation, and the reduction ratio of the amplitude of pulmonary venous $P_{CO_2}$ variation through the left heart (1962). Lamb *et al.* (1965) calculated oscillations of $P_{ACO_2}$ during the respiratory cycle in man at exercise and therefrom deduced arterial $P_{CO_2}$ ($Pa_{CO_2}$) oscillations, concluding that such oscillations of $Pa_{CO_2}$ did not per se influence ventilation. In 1968 Flumerfelt and Crandall developed a more complex calculation of $P_{AO_2}$ and $P_{ACO_2}$, considering pulsatile blood flow and sinusoidal ventilation, and showed the influence of pulsatility of blood flow on gas exchange. In calculations of moment-to-moment variations of alveolar gases Nye (1970) introduced a change of ventilatory pattern and proved that mean values of alveolar gases were a function of the ventilatory pattern, giving a theoretical basis for the change of alveolar-arterial $P_{O_2}$ or arterial-alveolar $P_{CO_2}$ differences with various ventilatory patterns such as discussed by Frumin *et al.* (1959) and Bergman (1963, 1967). Suwa and Bendixen (1972) combined sinusoidal ventilation and sinusoidally changing blood flow to show that negative mean alveolar-arterial $P_{O_2}$ and arterial-alveolar $P_{CO_2}$ differences could occur as a result of various combinations of flow and ventilatory pattern. In the same year (1972) Hlastala reported the instantaneous flux of gases in the lung for tidal ventilation with pulsatile blood flow, and showed that a model based on recruitment of new capillaries with each pulsation seemed to better fit the data of instantaneous gas exchange presented by Bosman *et al.* (1965).

Apart from these mathematical studies of alveolar gases, arterial pH was found to show oscillations connected with respiration by Nims and Marshall already in 1938. Thereafter the oscillations of arterial pH related to respiration were demonstrated by Bjurstedt (1946), Åström (1952), Honda and Ueda (1960), and Band *et al.* (1969a and b), and interpreted to reflect alveolar variations of $P_{CO_2}$ during the respiratory cycle. Apart from arterial pH oscillations with respiration Bjurstedt (1946) showed that arterial $O_2$ saturation was also oscillating with same frequency as respiration although the author did not comment on this phenomenon. An intentional study of the oscillations of arterial oxygenation was done by Bergman (1961) concerning their characteristics and the factors influencing them, and by Namur *et al.* (1961) with respect to the alternating stimulus for the respiratory center. Purves (1966) was the first to demonstrate oscillations in $P_{O_2}$ with a micro-electrode incorporated into a flow-through cuvette; he could also show the oscillations of $Pa_{O_2}$ in the high oxygenation range which had not been possible by oximetry. Recently Yokota and Kreuzer (1970) demonstrated $Pa_{O_2}$ oscillations with respiration from hypoxia to 100 % $O_2$ breathing; the amplitude was related to ventilatory frequency. Besides these authors described that even mixed venous $P_{O_2}$ changed cyclically with respiration.

There is general agreement that the arterial pH and $P_{O_2}$ oscillations with respiration reflect alveolar variations of $P_{CO_2}$ and $P_{O_2}$ during the respiratory cycle. However, the quantitative relationship between the magnitude of alveolar and arterial oscillations of $P_{O_2}$ during the respiratory cycle has not been studied before. There is a fundamental difference in the comparison of $P_{O_2}$ in alveoli and arteries; the magnitude of the $Pa_{O_2}$ oscillations can be measured continuously in situ, but this is not the case concerning $PA_{O_2}$. Hence numerous investigators, as mentioned above, tried to approach the moment-to-moment variation of alveolar gases on the basis of various assumptions and of simplified data, and therefore the differences in the assumptions or in the data could lead to deviating results. Since our first intention was to compare the amplitudes of $PA_{O_2}$ variation and of oscillating $Pa_{O_2}$ with respiration, it was necessary to develop a formula for the moment-to-moment variation of $PA_{O_2}$ from easily attainable experimental data while $Pa_{O_2}$ was measured continuously by a catheter $P_{O_2}$ electrode developed by Kimmich and Kreuzer (1969). The second step was to prove the validity of the calculated time course of $PA_{O_2}$ which is not directly accessible. Therefore we calculated the reduction ratio of the amplitude of $PA_{O_2}$ variation due to circulatory factors and compared it with the respiratory oscillation of $Pa_{O_2}$.

Mixed venous $P_{O_2}$ plays an important role in the gas exchange of the lung and was assumed to be constant during the respiratory cycle by all investigators. However, this is not the case in dogs breathing spontaneously or ventilated artificially, as demonstrated by Yokota and Kreuzer (1970). We described the possible influence of cyclically changing mixed venous $P_{O_2}$ on $PA_{O_2}$ as well as the characteristics of venous $P_{O_2}$ variation. The origin of venous $P_{O_2}$ variation was attributed to different timing of venous outflow from various organs as affected by respiration. However, venous outflow variation with respiration from abdominal organs, which is important

for the pattern of mixed venous $P_{O_2}$ variation, had not yet been elucidated sufficiently (particularly respiratory variation of hepatic outflow). Therefore we investigated the respiratory variation of venous return and proved the validity of our interpretation of venous $P_{O_2}$ variation with respiration. We also found that the divergent views on the behavior of hepatic outflow with respiration could be attributed to different experimental conditions.

(References are given after the Discussion)

# Chapter I

## ALVEOLAR OXYGEN TENSION IN ANESTHETIZED, ARTIFICIALLY VENTILATED DOGS*

**Abstract,** Moment-to-moment variation of effective alveolar $P_{O_2}$ ($P_{AeO_2}$) during the respiratory cycle was calculated based on a two-alveolar lung model in dogs anesthetized and pump-ventilated under various conditions induced by continuous infusion of sympathomimetics. Under fixed ventilation the amplitude of respiratory fluctuation of $P_{AeO_2}$ ($\Delta P_{AeO_2}$) increased with $\dot{V}_{O_2}$ ($\Delta P_{AeO_2} = 0.774 \cdot \dot{V}_{O_2} + 1.862$; $p < 0.001$) while $\Delta P_{AeO_2}$ did not show any correlation with $V_D/V_T$ or with the fraction of effective alveoli. Ideal alveolar $P_{O_2}$ ($P_{AiO_2}$) in the same situation was near the peak of fluctuating $P_{AeO_2}$, thus higher than mean effective alveolar $P_{O_2}$ ($\overline{P_{AeO_2}}$) by about 4 to 5 mm Hg. This difference of $P_{AiO_2}$ and $\overline{P_{AeO_2}}$ might be attributed to the difference in respiratory pattern, i.e., constant one-way flow as against periodic ventilation.

Alveolar oxygen tension
Oxygen fluctuations (respiratory)
Artificial ventilation
Sympathomimetics
Dog

Respiratory fluctuations of $P_{CO_2}$ and $P_{O_2}$ have been calculated by several authors (for $CO_2$: DuBois *et al.*, 1952; Chilton and Stacy, 1952; Yamamoto, 1960; Lamb *et al.*, 1965; for $O_2$: Chilton *et al.*, 1954; for both gases: Nye, 1970; Cumming and Lin, 1971; Suwa and Bendixen, 1972). Lamb *et al.* (1965) combined this sort of calculation with experiments and demonstrated changes of the amplitude of the alveolar $P_{CO_2}$ variations during exercise. Previous calculations of the alveolar $P_{O_2}$ oscillations were based on assumptions of ventilatory pattern and alveolar ventilation different from those presumed for the concept of ideal alveolar $P_{O_2}$ by Riley and Cournand (1949) and also from real volume changes. Recently Nye (1970) and Knelson *et al.* (1970) showed the importance of respiratory pattern for the computed mean effective alveolar $P_{O_2}$ by theoretical analysis and by experimental studies, respectively. It may be presumed that ideal alveolar $P_{O_2}$ based on constant flow ventilation should not be the same as mean effective alveolar $P_{O_2}$ calculated from periodic ventilation. In this paper we present data on the comparison between ideal and mean effective alveolar $P_{O_2}$ as well as variations of the amplitude of effective alveolar $P_{O_2}$ in various metabolic, circulatory, and respiratory conditions induced by infusion of sympathomimetics.

### THEORY

The fluctuations of alveolar $P_{O_2}$ were computed from a simple lung model as illustra-

* *Pflügers Archiv (1973), in press.*

ted in figure 1, consisting of a common airway and two alveolar compartments, one representing the effective alveolar space and the other the alveolar dead space. This simple model neglects secondary aerodynamic effects on gas flow as normally occurring in the lung. The following assumptions were made: 1) oxygen uptake ($\dot{V}_{O_2}$)

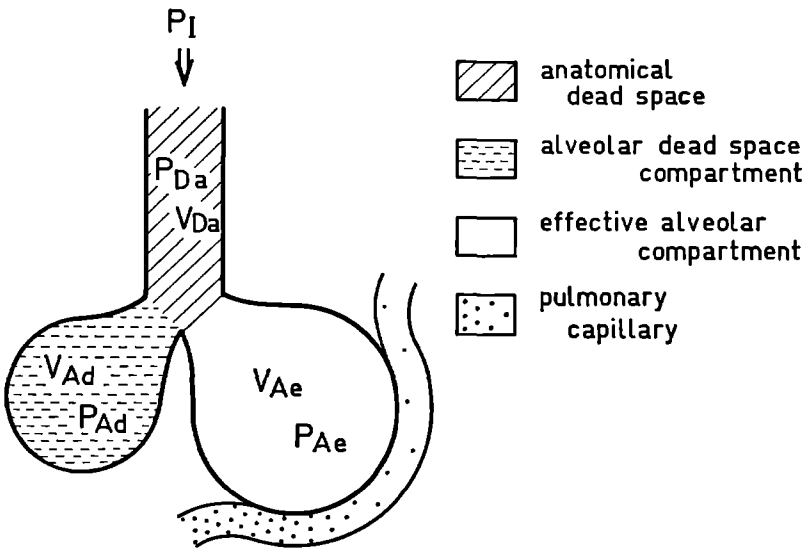



Fig. 1. Lung model consisting of a common airway (anatomical dead space) and two alveolar compartments, the effective or perfused alveolar compartment and the alveolar dead space or nonperfused compartment. Symbols are; $P_I$, $P_{Da}$, $P_{Ad}$, and $P_{Ae}$ = inspiratory, anatomical dead space, alveolar dead space, and effective alveolar partial pressure of oxygen, respectively; $V_{Da}$, $V_{Ad}$, and $V_{Ae}$ = anatomical dead space, alveolar dead space, and effective alveolar volume, respectively. Note that volumes and pressures in the alveolar compartments are varying according to the phase of respiration, but that $V_{Da}$ is constant and $P_{Da}$ here indicates the partial pressure in the anatomical dead space gas after expiration and to be reinhaled during the next inspiration.

and carbon dioxide output ($\dot{V}_{CO_2}$) are constant throughout the respiratory cycle, therefore exchange ratio (R) is also constant; 2) mixing of gases is instantaneous and gaseous composition is homogeneous in each compartment; 3) no gas exchange occurs between alveoli and airway otherwise than by gas flow; 4) anatomical dead space ($V_{Da}$) remains constant during the respiratory cycle; 5) functional residual capacity ($V_{FRC}$) remains unchanged throughout the experiment. The respiratory cycle is divided into five periods as shown in figure 2. PI: from the end of expiratory movement to the end of the entire expiratory phase or the onset of inspiration; thus during this period there is no ventilatory movement but the gas pressures in the effective alveolar compartment keep changing due to the continuous gas exchange with capillary blood only; this period has been introduced on the basis of experimental observations in our dog experiments (see below); PII: from the beginning of inspiration to the end of the wash-in of all gas from the anatomical dead space into

the alveoli; P III: from the inhalation of fresh air to the end of inspiration; P IV: from the beginning of expiration to the end of the phase during which any portion of alveolar gas leaving the alveolar space also leaves the body; PV: from this point to the end of ventilatory movement while the final portions of alveolar gas leaving the alveolar space fill the anatomical dead space and remain there to be reinhaled during

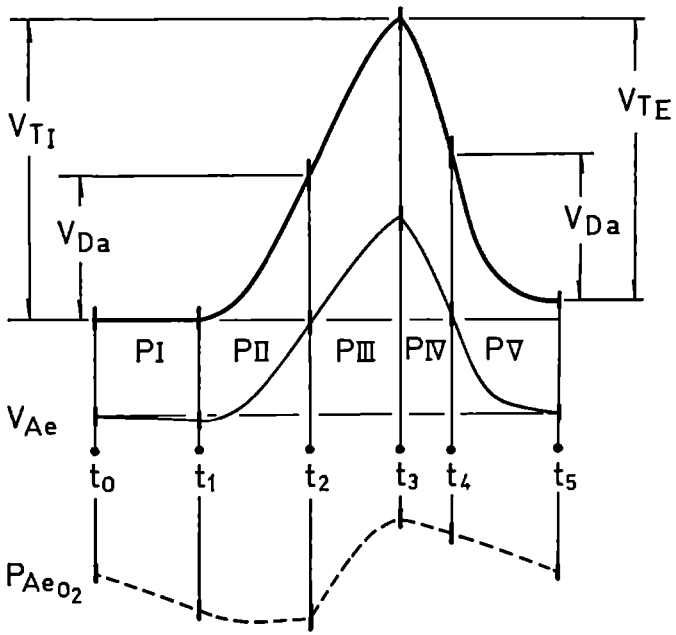



Fig. 2. Subdivision of respiratory cycle. The three curves show the respiratory cycle of, from top to bottom, spirometric volume change, effective alveolar volume ($V_{Ae}$), and effective alveolar oxygen pressure ($P_{Ae_{O_2}}$). The two lower curves are calculated. Other symbols are: $V_{TI}$ = inspiratory tidal volume; $V_{TE}$ = expiratory tidal volume; $V_{Da}$ = anatomical dead space volume; PI to PV = periods I to V; $t_0$ to $t_5$ = time points dividing periods. For details see text. Note that the intrapulmonary values of pressures and volumes at $t_5$ are the same as at $t_0$ whereas the spirometric volume (extrapulmonary) at $t_5$ is smaller than at $t_0$ if $R<1$ or $V_{TE}<V_{TI}$.

the next inspiration. The subdivision between P IV and P V is artificial in terms of the alveolar events during expiratory movement but had to be introduced in order to calculate the amount of oxygen in the anatomical dead space during P I because this anatomical dead space gas is reinhaled during the next inspiration.

Gas volumes and pressures were calculated in the following way, expressing volumes in BTPS if nothing else is mentioned. The fractional ratio of effective alveolar and alveolar dead space compartments to the total alveolar space was obtained in the same way as by Levy *et al.* (1965) and Workman *et al.* (1965). Thus $\alpha$ is the effective fraction of the total alveolar space:

$$\alpha = \frac{V_{Ae}}{V_{Ae} + V_{Ad}} \tag{1}$$

where $V_{Ae}$ is effective alveolar volume and $V_{Ad}$ is alveolar dead space volume. In fact this $\alpha$ was calculated as a fraction of effective alveolar ventilation to total ventilation; therefore we used this fraction to distribute tidal ventilation to effective alveolar and alveolar dead space compartments with a slight modification to compensate for the volume change due to gas exchange with lung capillary blood in the effective alveoli; $\alpha_I$ holds for the distribution of inspiratory gas to, and $\alpha_E$ for the contribution to expiratory gas from the effective alveoli (for derivation see below). Strictly speaking none of the values of $\alpha$ above is good enough to divide the lung volume into effective alveolar and alveolar dead space compartments during P I due to gas exchange in the effective alveolar space. Volume change of effective alveolar compartment during P I, however, is quite small in comparison with lung volume and tidal volume and, therefore, the type of $\alpha$ selected is immaterial for P I.

Thus we get for expiratory pause and inspiration (P I to P III):

$$t_o \leqslant t \leqslant t_3 \qquad \frac{dV_{Ae,\,t}}{dt} = \alpha_I \cdot \frac{dV_t}{dt} - \eta \tag{2}$$

$$\frac{dV_{Ad,\,t}}{dt} = (1 - \alpha_I) \cdot \frac{dV_t}{dt} \tag{3}$$

where $V_t$ = inspiratory volume (subscript t referring to any time period t), and $\eta = \dot{V}_{O2} \cdot (1 - R)$, the volume change per unit time due to gas exchange with capillary blood. Similarly we have for expiration (P IV and P V):

$$t_3 \leqslant t \leqslant t_5 \qquad \frac{dV_{Ae,\,t}}{dt} = -\alpha_E \cdot \frac{dV_t}{dt} - \eta \tag{4}$$

$$\frac{dV_{Ad,\,t}}{dt} = -(1 - \alpha_E) \cdot \frac{dV_t}{dt} \tag{5}$$

where $V_t$ = expiratory volume.

$P_{O2}$ was calculated from the gas law, $n \cdot R \cdot T = P \cdot V$. Since R is the universal gas constant and T, the absolute temperature, is also taken constant, all changes in $P \cdot V$ reflect the change in amount of oxygen (n). During P I the amount of oxygen is changed only in the effective alveolar space due to gas exchange with capillary blood:

$$t_o \leqslant t \leqslant t_1 \qquad \frac{d}{dt}(P_{Ae,\,t} \cdot V_{Ae,\,t}) = -\varphi \tag{6}$$

where $P_{Ae}$ represents the $P_{O2}$ in the effective alveolar space and $\varphi = \dot{V}_{O2} \cdot (P_B - P_{H2O})$, reflecting the amount of oxygen taken up by capillary blood per unit time;

$P_B$ = barometric pressure; $P_{H2O}$ = water vapor pressure at body temperature. We can derive for the reinspiration of anatomical dead space gas (P II):

$$t_1 \leqslant t \leqslant t_2$$

$$\frac{d}{dt}(P_{Ae,t} \cdot V_{Ae,t}) = P_{Da} \cdot \alpha_I \cdot \frac{dV_t}{dt} - \varphi \tag{7}$$

$$\frac{d}{dt}(P_{Ad,t} \cdot V_{Ad,t}) = P_{Da} \cdot (1 - \alpha_I) \cdot \frac{dV_t}{dt} \tag{8}$$

where $P_{Da}$ represents the $P_{O2}$ in the anatomical dead space after the end of the previous expiration and $P_{Ad}$ the $P_{O2}$ in the alveolar dead space. After washing in the anatomical dead space gas, fresh air reaches the alveoli (P III):

$$t_2 \leqslant t \leqslant t_3$$

$$\frac{d}{dt}(P_{Ae,t} \cdot V_{Ae,t}) = P_I \cdot \alpha_I \cdot \frac{dV_t}{dt} - \varphi \tag{9}$$

$$\frac{d}{dt}(P_{Ad,t} \cdot V_{Ad,t}) = P_I \cdot (1 - \alpha_I) \cdot \frac{dV_t}{dt} \tag{10}$$

where $P_I$ is the $P_{O2}$ of inspiratory gas. Finally for expiration (P IV and P V):

$$t_3 \leqslant t \leqslant t_5$$

$$\frac{d}{dt}(P_{Ae,t} \cdot V_{Ae,t}) = -P_{Ae,t} \cdot \alpha_E \cdot \frac{dV_t}{dt} - \varphi \tag{11}$$

$$\frac{d}{dt}(P_{Ad,t} \cdot V_{Ad,t}) = -P_{Ad,t} \cdot (1 - \alpha_E) \cdot \frac{dV_t}{dt} \tag{12}$$

During P V expiration fills the anatomical dead space with gas to be reinhaled during the next inspiration. This endexpiratory gas in the anatomical dead space which leaves the alveoli between $t_4$ and $t_5$ but does not appear outside of the body has the following amount of oxygen:

$$t_4 \leqslant t \leqslant t_5 \qquad \frac{d}{dt}(P \cdot V)_{Da} = P_{Ae,t} \cdot \alpha_E \cdot \frac{dV_t}{dt} + P_{Ad,t} \cdot (1 - \alpha_E) \cdot \frac{dV_t}{dt} \tag{13}$$

where V = expired volume and $(P \cdot V)_{Da}$ = amount of oxygen accumulated in the anatomical dead space during P V and reaching $P_{Da} \cdot V_{Da}$ at $t_5$.

These equations are now solved for each period. For P I, the endexpiratory pause, we get by solving (2) and (6):

$$t_0 \leqslant t \leqslant t_1$$

$$V_{Ae,t} = V_{Ae,t_0} - \eta \cdot (t - t_0) \tag{14}$$

$$P_{Ae,t} \cdot V_{Ae,t} = P_{Ae,t_0} \cdot V_{Ae,t_0} - \varphi \cdot (t - t_0) \tag{15}$$

Since there is no gas exchange in the alveolar dead space, its volume and pressure remain unchanged during this period. In P II we get from (2), (3), (7), and (8) for the effective and alveolar dead space compartments, respectively:

$$V_{Ae,\,t} = V_{Ae,\,t_0} + \alpha_I \,.\, V_t - \eta \,.\, (t - t_0) \tag{16}$$

$$P_{Ae,\,t} \,.\, V_{Ae,\,t} = P_{Ae,\,t_0} \,.\, V_{Ae,\,t_0} + P_{Da} \,.\, \alpha_I \,.\, V_t - \varphi \,.\, (t - t_0) \tag{17}$$

$t_1 \leqslant t \leqslant t_2$

$$V_{Ad,\,t} = V_{Ad,\,t_0} + (1 - \alpha_I) \,.\, V_t \tag{18}$$

$$P_{Ad,\,t} \,.\, V_{Ad,\,t} = P_{Ad,\,t_0} \,.\, V_{Ad,\,t_0} + P_{Da} \,.\, (1 - \alpha_I) \,.\, V_t \tag{19}$$

In P III, for the volume changes (16) and (18) still hold, but now fresh air reaches both alveolar compartments:

$$P_{Ae,\,t} \,.\, V_{Ae,\,t} = P_{Ae,\,t_0} \,.\, V_{Ae,\,t_0} + P_{Da} \,.\, \alpha_I \,.\, V_{Da} + P_I \,.\, \alpha_I \,.\, (V_t - V_{Da}) - \varphi \,.\, (t - t_0) \tag{20}$$

$t_2 \leqslant t \leqslant t_3$

$$P_{Ad,\,t} \,.\, V_{Ad,\,t} = P_{Ad,\,t_0} \,.\, V_{Ad,\,t_0} + P_{Da} \,.\, (1 - \alpha_I) \,.\, V_{Da} + P_I \,.\, (1 - \alpha_I) \,.\, (V_t - V_{Da}) \tag{21}$$

During the expiratory periods (P IV and P V) we get from (4) and (5) for the volumes of both alveolar compartments:

$$V_{Ae,\,t} = V_{Ae,\,t_0} + \alpha_I \,.\, V_{TI} - \alpha_E \,.\, V_t - \eta \,.\, (t - t_0) \tag{22}$$

$t_3 \leqslant t \leqslant t_5$

$$V_{Ad,\,t} = V_{Ad,\,t_0} + (1 - \alpha_I) \,.\, V_{TI} - (1 - \alpha_E) \,.\, V_t \tag{23}$$

where now $V_{TI}$ = inspiratory tidal volume and $V_t$ = expiratory volume for any time period. Since there is no gas exchange in the alveolar dead space, $P_{Ad}$ does not change during these periods and the alveolar dead space diminishes only its volume. By differentiating the product $P_{Ae} \,.\, V_{Ae}$ from (11) and substituting for $\frac{dV_{Ae,\,t}}{dt}$ from (4) we get:

$$\frac{d}{dt}(P_{Ae,\,t} \,.\, V_{Ae,\,t}) = V_{Ae,\,t} \,.\, \frac{dP_{Ae,\,t}}{dt} + P_{Ae,\,t} \,.\, \left(-\alpha_E \,.\, \frac{dV_t}{dt} - \eta\right) \tag{24}$$

Substituting the left term of (24) from (11), and rearranging:

$$V_{Ae,\,t} \,.\, \frac{dP_{Ae,\,t}}{dt} = \eta \,.\, P_{Ae,\,t} - \varphi \tag{25}$$

which may be solved to give:

$$P_{Ae,\,t} = P_{Ae,\,t_5} + \left(\frac{\varphi}{\eta} - P_{Ae,\,t_5}\right) \cdot \left(1 - e^{-\int_t^{t_5} dt \frac{\eta}{V_{Ae,\,t}}}\right) \tag{26}$$

The final values of intrapulmonary volume and pressure must be the same as the starting values at $t_0$, or $V_{Ad,\,t} = V_{Ad,\,t_0}$ in (23). Therefore equation (23) leads to ($V_t$ now becomes $V_{TE}$):

$$(1 - \alpha_I) \cdot V_{TI} = (1 - \alpha_E) \cdot V_{TE} \tag{27}$$

and by adding (22) and (23) we get:

$$V_{TI} = V_{TE} + \eta \cdot (t_5 - t_0) \tag{28}$$

$V_{FRC}$ is defined as the lung volume just before the beginning of inspiration, i.e., at $t_1$, therefore:

$$V_{FRC} = V_{Ae,\,t_1} + V_{Ad,\,t_1} + V_{Da} \tag{29}$$

If the volume ratio $V_{Ae}/V_{Ad}$ is assumed to be the same at the start and at the end of inspiration, we get:

$$V_{Ae,\,t_1} = (V_{FRC} - V_{Da}) \cdot \frac{\alpha_I \cdot V_{TI} - \eta \cdot (t_3 - t_1)}{V_{TI} - \eta \cdot (t_3 - t_1)} \tag{30}$$

Since $P_{Ad}$, which had slightly decreased during reinspiration of anatomical dead space gas, has been restored by inhalation of fresh air at $t_3$, we derive from (18) and (21):

$$P_{Ad,\,t_0} \cdot V_{TI} = P_{Da} \cdot V_{Da} + P_I \cdot (V_{TI} - V_{Da}) \tag{31}$$

A similar manipulation of $P_{Ae,\,t_3}$ from (20) and (26) with (31) leads to:

$$P_{Ae,\,t_0} \cdot (e_3\, V_{Ae,\,t_3} - V_{Ae,\,t_0}) = P_{Ad,\,t_0} \cdot \alpha_I \cdot V_{TI} - \varphi \cdot (t_3 - t_0) - \frac{\varphi}{\eta} \cdot (1 - e_3) \cdot V_{Ae,\,t_3} \tag{32}$$

where $V_{Ae,\,t_3}$ is obtained by (16) and $e_3 = e^{-\int_{t_3}^{t_5} dt \frac{\eta}{V_{Ae,\,t}}}$. Integrating the sum of equations (11) and (13) from $t_4$ to $t_5$ and calculating $P_{Ae,\,t_4}$ by (26) provides:

$$P_{Ae,\,t_0} \cdot (e_4 \cdot V_{Ae,\,t_0} - V_{Ae,\,t_0}) + P_{Ad,\,t_0} \cdot (1 - \alpha_E) \cdot V_{Da}$$

$$= P_{Da} \cdot V_{Da} + \varphi \cdot (t_5 - t_4) - \frac{\varphi}{\eta} \cdot (1 - e_4) \cdot V_{Ae,\,t_4} \qquad (33)$$

where $e_4$ is the same expression as $e_3$ but from $t_4$ to $t_5$, and $V_{Ae,\,t_4}$ is obtained from (22). At $t_4$ the expired volume equals $V_{TE} - V_{Da}$. Thus we obtained three equations (31), (32) and (33) to be solved for three unknown boundary conditions, $P_{Ae,\,t_0}$, $P_{Ad,\,t_0}$, and $P_{Da}$.

The distribution factor $\alpha_I$ is calculated from the following consideration for $CO_2$. Total $CO_2$ leaving both alveolar spaces during expiration equals the sum of the expired portion leaving the body and that remaining in the anatomical dead space. When realizing that the amount of $CO_2$ coming from the alveolar dead space is exactly the same as that inhaled into it before:

$$\overline{P_{Ae}}_{CO_2} \cdot \alpha_E \cdot V_{TE} + P_{Da_{CO_2}} \cdot (1 - \alpha_I) \cdot V_{Da} = P_{Da_{CO_2}} \cdot V_{Da} + \overline{P_E}_{CO} \cdot V_{TE} \qquad (34)$$

where $\overline{P_{Ae}}_{CO_2}$ is the mean effective alveolar $P_{CO_2}$, and $\overline{P_E}_{CO_2}$ is the mean expired $P_{CO_2}$. Equation (34) is the same expression for $V_{Da}$ as Bohr's equation but for a two-alveolar lung model. Together with (27) equation (34) leads to:

$$1 - \alpha_I = \frac{\overline{P_{Ae}}_{CO_2} - P_{Da_{CO_2}}}{\overline{P_{Ae}}_{CO_2} \cdot V_{TI}/V_{TE} - P_{Da_{CO_2}} + \overline{P_E}_{CO_2}} \qquad (35)$$

$\alpha_E$ is obtained similarly from (27) and (35). $V_{Da}$ is calculated from Bohr's equation assuming endtidal $P_{CO_2}$ as representative for mean total alveolar $P_{CO_2}$ and for $P_{Da_{CO_2}}$ in the equations above, and $\overline{P_{Ae}}_{CO_2}$ is assumed to equal $Pa_{CO_2}$ (neglecting the shunt effect). Since in a constant-flow model mean total alveolar $P_{CO_2}$ equals $P_{Da_{CO_2}}$ in P I, equation (35) becomes the same as that derived by Levy *et al.* (1965) and Workman *et al.* (1965) except for $V_{TI}/V_{TE}$ in the denominator.

## Methods

Experiments were performed in 15 dogs of either sex, weighing 12 to 23 kg. The dog was premedicated with acepromazine 1 mg/kg and anesthetized with chloralose-urethane (for induction 25–50 mg/kg and 125–250 mg/kg, and for maintenance 5–10 mg/kg/h and 25–50 mg/kg/h, respectively). The animal in supine position was ventilated by a Harvard pump (model 607) through a cuffed tracheal tube, with ventilatory volume adjusted to obtain about 4 % endtidal $CO_2$ at the beginning of the experiment; breathing frequency was 12 to 18/min; this ventilatory volume was maintained throughout the experiment. Spontaneous breathing was suppressed by continuous infusion of Alloferin (6 mg/h, Roche).

Respiratory pattern was recorded by a pneumotachograph and respiratory $P_{O_2}$ and $P_{CO_2}$ were monitored by a catheter $P_{O_2}$ electrode (Schuler and Kreuzer, 1967) and an

infrared $CO_2$ analyzer, respectively. Blood $P_{O2}$ was continuously measured in the proximal descending aorta and in the main pulmonary artery by catheter $P_{O2}$ electrodes (Kimmich and Kreuzer, 1969). Hollow catheters were introduced under fluoroscopic guidance for arterial and mixed venous blood sampling, pressure measurement by Statham strain gauges, and infusion of muscle relaxant and sympathomimetic drugs. Blood clotting was prevented by heparin administration (2 ml of 5000 units/ml at the beginning and again 3 to 4 hours later). Pneumotachogram, respiratory $P_{O2}$ and $P_{CO2}$, blood $P_{O2}$, and blood pressure were all recorded by a Honeywell Visicorder 1108.

After two sets of simultaneously taken control samples of arterial and mixed venous blood and expiratory gas, the dog received a continuous infusion of sympathomimetic drug (noradrenaline 5 µg/kg/min, adrenaline 5 µg/kg/min, isoprenaline 1 µg/kg/min, or TH1165a 0.5 µg/kg/min (Boehringer)) for 45 to 60 min in order to induce changes in respiratory parameters such as $\dot{V}_{O2}$, anatomical dead space, pulmonary circulation, etc., and consequently in the fluctuations of $P_{Ae_{O2}}$. Blood and gas samples were collected about every 15 min during the infusion of sympathomimetic drug and the last samples were taken 15 to 20 min after the end of infusion. The dog received isotonic bicarbonate solution to readjust the pH to normal range and was allowed about 60 min to reach a new steady state before the second infusion of sympathomimetic was given. At the end of the experiment the animal was given a hypoxic gas mixture to get calibration points of the blood and gas catheter $P_{O2}$ electrodes.

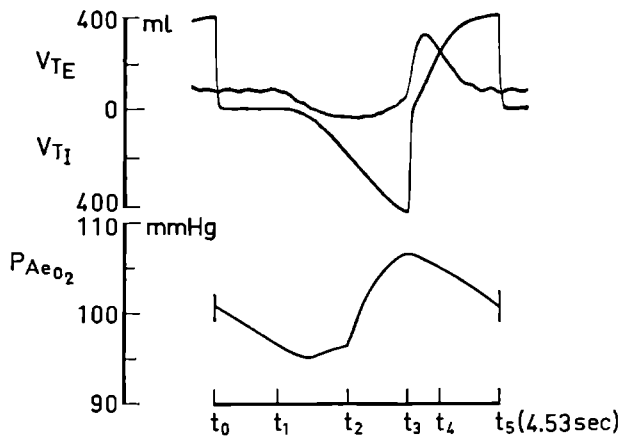
Blood samples were analyzed instantaneously for $P_{O2}$, $P_{CO2}$, and pH by a Radiometer Gasmonitor (type PHA 927b, Copenhagen) and by a Radiometer pH meter (type PHM 22r), respectively. When the body temperature of the dog varied from that of the instruments blood gas tensions and pH were corrected according to Kelman and Nunn (1966). Expired gas samples were analyzed for $O_2$ and $CO_2$ by a paramagnetic $O_2$ analyzer and by an infrared $CO_2$ analyzer, respectively. FRC was measured by the open nitrogen method. Inspiratory and expiratory volumes were obtained from the integrated pneumotachogram corrected for BTPS from expired gas collected during several minutes. Calculation of $P_{Ae}$ was conducted by a digital computor (IBM 370) programmed in FORTRAN for every 0.2 sec and at $t_0$, $t_1$, $t_2$, $t_3$, and $t_4$, together with mean $P_{Ae}$ obtained by dividing the fluctuating $P_{Ae}$ horizontally into equal areas.

Statistical significance of differences of variables was computed by Student's t test between control period and sympathomimetic infusion in each group of sympathomimetics or between groups with different sympathomimetics following Snedecor and Cochran (1968). Also the significance of correlation was assessed by Student's t test between the amplitude of $P_{Ae_{O2}}$ and the other variables. The limit of significance was assumed at $p = 0.05$.

## Results

Figure 3 shows an example of calculated $P_{Ae_{O2}}$ together with a record of the pneumo-

tachogram and its integrated volume, also presenting other data used for the computation of the $P_{AeO_2}$. The difference of $\alpha_I$ and $\alpha_E$ was less than 0.001 in all computations of $P_{AeO_2}$. $P_{AeO_2}$ always reaches its maximum value at the end of inspiration whereas the minimum is located between the beginning of inspiration and the end of washing in of dead space gas, depending on a combination of changes of various factors occurring in equations (16) and (17).




Dog 17.5 kg
$P_B$ = 744.4 mmHg $P_{H_2O}$ = 50.2 mmHg $B_T$ = 38.2°C
$V_{FRC}$ = 751 ml $\dot{V}_{O_2}$ = 253 ml/sec R = 0.96
$P_{a_{CO_2}}$ = 37.7 mmHg $P_{\bar{E}_{CO_2}}$ = 17.7 mmHg $P_{CO_2}^{*}$ = 27.5 mmHg
$\alpha_I$ = 0.6232 $\alpha_E$ = 0.6228

Fig. 3. Example of computed effective alveolar $P_{O_2}$ ($P_{AeO_2}$) with data used for its calculation. Volume change was obtained from the integrated pneumotachogram as shown in top panel. $P_{CO_2}^{*}$ is endtial $P_{CO_2}$. $\alpha_I$ and $\alpha_E$ were obtained as described in the text.

Figure 4 demonstrates the mean values of the principal variables determining $P_{AeO_2}$ under fixed ventilation and the amplitude of the alveolar $P_{O_2}$ fluctuation ($\Delta P_{AeO_2}$) at various sampling times for different sympathomimetics. There is in all cases a tendency for an increase of $\dot{V}_{O_2}$, anatomical dead space ratio, and $\Delta P_{AeO_2}$ during infusion of sympathomimetics although statistical significance could not be proven for the increase during infusion and for the differences between various sympathomimetics due to wide individual variations. On the other hand $\alpha$ did not show any distinct tendency in all cases. The relationship between the changes of $\Delta P_{AeO_2}$ and other factors is not clear-cut on the average except for $\dot{V}_{O_2}$ which showed a significant correlation with $\Delta P_{AeO_2}$; the regression line is given by $\Delta P_{AeO_2} = 0.774 \dot{V}_{O_2} + 1.862$ ($p < 0.001$, $n = 185$, $\Delta P_{AeO_2}$ in mm Hg and $\dot{V}_{O_2}$ in ml STPD per breath because this is conventional).

As indicated in figure 5 for all sympathomimetics ideal alveolar oxygen pressure ($P_{Ai_{O_2}}$) obtained from the conventional alveolar equation is always higher than mean effective alveolar oxygen pressure ($P_{\overline{Ae}_{O_2}}$) as derived from dividing the respiratory fluctuation of $P_{Ae_{O_2}}$ into two equal areas; the difference was of the order of 4 mm Hg.

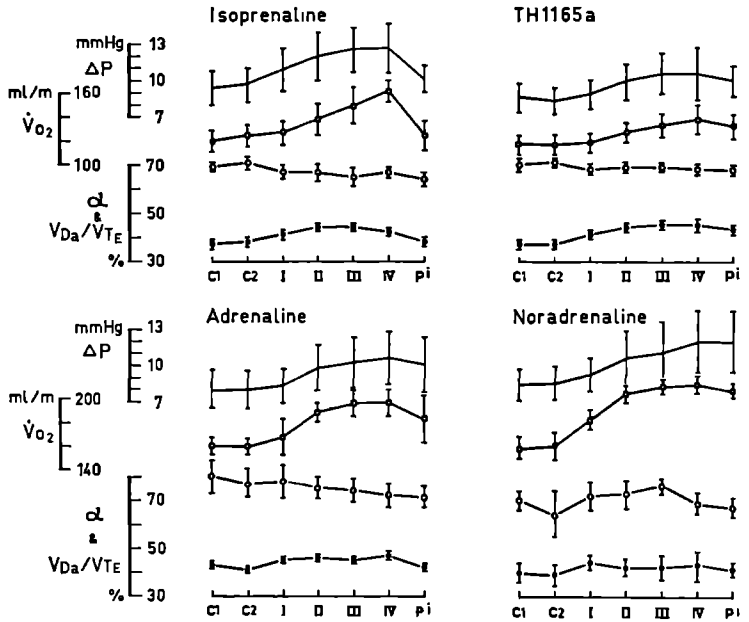



Fig. 4. Changes of mean values of the amplitude of effective alveolar $P_{O_2}$ ($\triangle$ P), oxygen uptake in ml STPD/min ($\dot{V}_{O_2}$), fraction of effective alveolar compartment ($\alpha$), and anatomical dead space ratio ($V_{Da}/V_{TE}$) with $\pm$ one standard deviation (vertical bars) in the course of sympathomimetic drug infusion. Symbols on abscissas are; c1 and c2 = control values; I to IV = sample values during sympathomimetic drug infusion; pi = post-infusion value. Data for isoprenaline, TH1165a, adrenaline, and noradrenaline were obtained from 10, 9, 4, and 3 experiments, respectively.

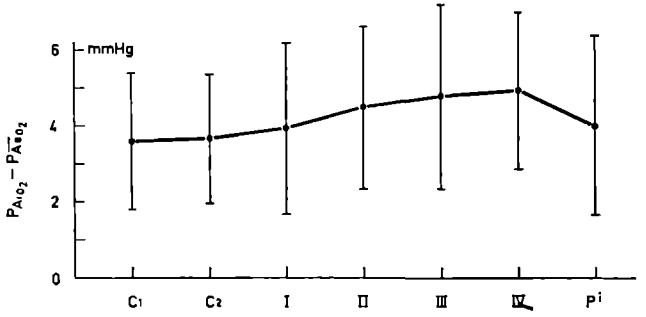



Fig. 5. Comparison of ideal alveolar $P_{O_2}$ ($P_{Ai_{O_2}}$) and mean effective alveolar $P_{O_2}$ ($P_{\overline{Ae}_{O_2}}$) in terms of ($P_{Ai_{O_2}} - P_{\overline{Ae}_{O_2}}$) presented as mean values during the course of sympathomimetic drug infusion. c1 and c2 = control values; I to IV = values during infusion; pi = post-infusion value. Vertical bars show $\pm$ one standard deviation.

There was a tendency to an increase of this difference during infusion but variations from one sampling time to another and from case to case were rather high so that no statistical significance could be assessed for changes of this difference in time and among sympathomimetics. However, the variation of ($P_{Ai O_2} - \bar{P_{Ae}}_{O_2}$) during infusion of sympathomimetic showed a significant positive correlation with $\Delta P_{Ae O_2}$ and $\dot{V}_{O_2}$ in 20 and 16 out of 26 infusion runs, respectively.

## Discussion

The ideal alveolar gas concept of Riley and Cournand (1949) has been widely applied in pulmonary physiology and numerous data of the alveolar-arterial oxygen pressure difference have been based on the conventional alveolar air equation to compute representative alveolar oxygen pressure by inserting $P_{aCO_2}$. Severinghaus and Stupfel (1957), however, pointed out that physiological dead space ventilation from Bohr's equation using $P_{aCO_2}$ underestimates alveolar dead space ventilation, i.e., overestimates effective alveolar ventilation. Ross and Farhi (1960) reported that reinspiration of dead space gas modifies the alveolar gas and lowers maximal alveolar $P_{O_2}$. Since our calculation of $P_{Ae O_2}$ uses another estimate of effective alveolar ventilation and takes the dead space gas into accout, a different mean alveolar $P_{O_2}$ should result. In order to demonstrate this difference we also estimated the ideal alveolar $P_{O_2}$ with our alveolar ventilation ratio and with reinspiration of anatomical dead space gas as shown above but maintaining constant ventilation as assumed by Riley and Cournand (1949). The alveolar gas equation of Otis (1964) was applied:

$$P_{A O_2} = P_{I O_2} - \frac{\dot{V}_{O_2}}{\dot{V}_A} \cdot (P_B - P_{H_2O}) + P_{I O_2} \cdot (1 - R) \cdot \frac{\dot{V}_{O_2}}{\dot{V}_A} \qquad (36)$$

where $P_{A O_2}$ and $\dot{V}_A$ are assumed to correspond to our $P_{Ae}$ and $\dot{V}_A$, respectively, for constant ventilation. $P_{I O_2}$ was replaced for reinspiration of dead space gas by

$$P_{I O_2} = \frac{P_{A CO_2} - \bar{P_E}_{CO_2}}{P_{A CO_2}} \cdot (P_{I O_2} - P_{Da O_2}) \cdot \frac{V_{T_E}}{V_{T_I}},$$

where $P_{Da O_2}$ was obtained during calculation of $P_{Ae}$ above, and $\dot{V}_A$ was replaced by $\dot{V}_E \cdot \{\bar{P_E}_{CO_2} / (P_{aCO_2} - P_{A CO_2} + \bar{P_E}_{CO_2})\}$ which equals $\dot{V}_E \cdot \alpha$; $P_{A CO_2}$ is the mean total alveolar $P_{CO_2}$, $\bar{P_E}_{CO_2}$ the mean expiratory $P_{CO_2}$, $P_{Da O_2}$ the anatomical dead space $P_{O_2}$, and $P_{aCO_2}$ the arterial $P_{CO_2}$. We used, however, endtidal $P_{CO_2}$ in place of $P_{A CO_2}$. Calculated mean $P_{A O_2}$ was now very close to the conventional $P_{Ai O_2}$. This is shown by subtracting the ideal alveolar air equation from (36) with substitution for $P_{I O_2}$ and $\dot{V}_A$ and rearranging:

$$P_{AO_2} - P_{AiO_2} = -(P_{ACO_2} - \bar{P}_{ECO_2}) \cdot \left\{ \frac{V_{TE}}{V_{TI}} \cdot \frac{P_{IO_2} - P_{DaO_2}}{P_{ACO_2}} - \frac{1}{R} + \left(\frac{1}{R} - 1\right) \cdot F_{IO_2} \right\} \qquad (37)$$

where $P_{AO_2}$ = alveolar $P_{O_2}$ in (36) with substitution, and $F_{IO_2}$ = fractional concentration of oxygen in inspiratory gas. All the quotients in the large parenthesis of (37) are close to 1, therefore ($P_{AO_2} - P_{AiO_2}$) is nearly zero. When taking R = 1 we derive from (37) (with $\frac{P_{ACO_2} - \bar{P}_{ECO_2}}{P_{ACO_2}} = \frac{V_{Da}}{V_{TE}}$ and $V_{TI} = V_{TE}$ when R = 1):

$$P_{AO_2} - P_{AiO_2} = -\frac{V_{Da}}{V_{TE}}(P_{IO_2} - P_{DaO_2} - P_{ACO_2}) \qquad (38)$$

Here $P_{DaO_2}$ equals mean total alveolar $P_{O_2}$ in the constant-flow pattern and the sum of this and $P_{ACO_2}$ is equal to $P_{IO_2}$ for R = 1 so that equation (38) becomes zero. Our substitution by endtidal pressure values, of course, does not give an exact result but the error in (38) must be small since it is multiplied by the anatomical dead space ratio which is much smaller than one (about 0.4 here). This implies that the difference between $P_{AiO_2}$ and $\bar{P}_{AeO_2}$ is not due to the difference in alveolar ventilation ratio and reinspiration of anatomical dead space gas.

The principal difference therefore resides in the fact that the ideal alveolar gas equation is based on constant oneway ventilation whereas we took periodic ventilation into account. The influence of respiratory pattern on alveolar $P_{O_2}$ was evaluated theoretically by Nye (1970) and experimentally by Knelson *et al.* (1970) with results similar to ours. Figure 6 shows the influence of ventilatory pattern on $P_{AeO_2}$ and therefore $\bar{P}_{AeO_2}$ at two sampling times during one experiment. Rectangular ventilation (broken lines) provides a higher $\bar{P}_{AeO_2}$ than the actual respiratory pattern and also a slightly higher value than $P_{AiO_2}$ (broken-dotted lines in figure 6). $P_{AiO_2}$ is near the peak of $P_{AeO_2}$; therefore ($P_{AiO_2} - \bar{P}_{AeO_2}$) is practically half the amplitude of $\Delta P_{AeO_2}$ and must change with $\dot{V}_{O_2}$ as well (see above). Thus we may conclude that the difference between $P_{AiO_2}$ and $\bar{P}_{AeO_2}$ is due to the difference in ventilatory pattern. Similar results on a single alveolar model were attributed, however, to reinhalation of anatomical dead space gas by Suwa and Bendixen (1972). During spontaneous respiration (not shown here) this difference between $P_{AiO_2}$ and $\bar{P}_{AeO_2}$ may be smaller, i.e., $\bar{P}_{AeO_2}$ would be higher, since artificial ventilation with muscular relaxant as applied here is accompanied by a sharper and narrower ventilatory profile (compared with spontaneous respiration) which would be expected to result in a lower $\bar{P}_{AeO_2}$; in other words, the spontaneous respiratory pattern might be presumed to be located between the peaked and rectangular curves of $V_{Ae}$ in figure 6.

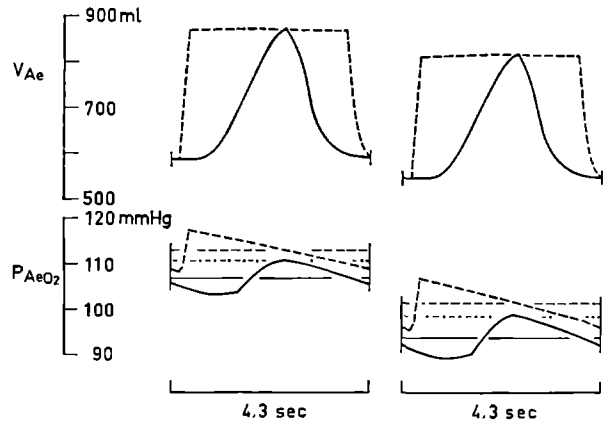



Fig. 6. Influence of respiratory pattern on mean effective alveolar $P_{O_2}$ in two different periods (right and left panels) in one dog. Curves in solid lines show effective alveolar volumes ($V_{Ae}$) in upper panels and effective alveolar $P_{O_2}$ ($P_{AeO_2}$) in lower ones. Broken curves in upper panels show rectangular effective alveolar volume change and lower ones effective alveolar $P_{O_2}$ obtained from this ventilatory pattern with the same data otherwise. Horizontal lines in lower panels are mean effective alveolar $P_{O_2}$ for rectangular ventilatory pattern (broken lines), ideal alveolar $P_{O_2}$ (broken-dotted lines), and mean effective alveolar $P_{O_2}$ for peaked pattern (solid lines), respectively. For discussion see text.

We used endtidal $P_{CO_2}$ for $P_{ACO_2}$ in order to get anatomical dead space and effective alveolar fraction. Since endtidal $P_{CO_2}$ is smaller than mean total alveolar $P_{CO_2}$ with the ventilatory pattern applied here, we systematically underestimated anatomical dead space and also effective alveolar fraction by taking the endtidal value for $P_{ACO_2}$ and $P_{DaCO_2}$. In order to evaluate the influence of this underestimation of $P_{ACO_2}$ on $P_{AeO_2}$ we corrected the endtidal $P_{CO_2}$ by a factor $\alpha \cdot R \cdot (P_{AeO_2, t_4} - \overline{P_{AeO_2}})$ (assuming that $P_{AeCO_2}$ has the same time course as $P_{AeO_2}$) and recalculated $P_{AeO_2}$ and $\overline{P_{AeO_2}}$. This calculation showed that $\overline{P_{AeO_2}}$ was practically unaffected (maximal increase of 0.3 mm Hg) whereas $\Delta P_{AeO_2}$ was reduced by maximally 10 %. This correction of $P_{ACO_2}$ increased $\alpha$ by 5 to 8 % and also increased the anatomical dead space but these variations cancel each other so that the substitution of $P_{ACO_2}$ by endtidal $P_{CO_2}$ is of only minor consequence. As may be seen from figure 6, the use of the endtidal values would, on the other hand, overestimate $P_{ACO_2}$ in case of the rectangular pattern; therefore it might be advisable to use a rather high breathing frequency to reduce the endtidal to mean total alveolar $P_{CO_2}$ difference by decreasing the respiratory fluctuations in the effective alveolar space.

We have assumed that the anatomical dead space gas is homogeneous and the anatomical dead space volume remains constant during the respiratory cycle. Concerning the first assumption, however, it might be more reasonable to assume that anatomical dead space gas remains stratified because we assumed the inspiratory gas to have an undisturbed sharp front during its passage through the airway. A sample calculation showed that inhalation of stratified anatomical dead space gas did not

alter the pattern of $P_{Ae}O_2$ noticeably. Concerning the second assumption of a constant anatomical dead space volume, however, it is well known that it changes with lung volume (Fowler, 1948; Severinghaus and Stupfel, 1957; Shepard *et al.*, 1957) and decreases during breathholding (Fowler, 1947; Bartels *et al.*, 1954; Shepard *et al.*, 1957; Norris, 1967). Thus it is quite conceivable that anatomical dead space varies by two factors: variation of true anatomical space of the airway with lung volume and tendency of the space of the airway to decrease its functional dead volume due to diffusion of gases seen as a decrease of anatomical dead space during breathholding. At present we cannot estimate the change of anatomical dead space during the respiratory cycle by conventional methods.

The effective alveolar fraction $\alpha$ may be regarded as another measure of the distribution of blood to the perfused alveoli and therefore will follow changes in lung volume, an increase of lung volume being accompanied by a less even distribution of blood flow and vice versa (Pain and West, 1966; Hughes *et al.*, 1968a and b). An increase of alveolar dead space with increasing transpulmonary pressure has been described by Strieder *et al.* (1970). When assuming that this also holds during the respiratory cycle, $\alpha$ will decrease with inspiration and increase with expiration; therefore $\Delta P_{Ae}O_2$ should also be affected although we did not evaluate this effect. The influence of varying R during respiration (Ferris *et al.*, 1946; Otis *et al.*, 1948; Stacy and Kydd, 1950; Chilton *et al.*, 1954; Nye, 1970; Suwa and Bendixen, 1972) was not taken into account in our calculations since inspection of equations (14) to (22) will show that the term $\eta \cdot t$ is small compared with the other terms.

Respiratory variation of alveolar capillary blood flow has been shown by DuBois and Marshall (1957) as well as Vermeire and Butler (1965). This factor is rather variable and of unknown magnitude in the dog and oxygen uptake does not only depend on pulmonary blood flow but also on mixed venous $P_{O_2}$ both of which vary cyclically with respiration. Yokota and Kreuzer (1972) reported that mixed venous $P_{O_2}$ increases during inspiration and decreases during expiration with spontaneous breathing and this pattern is reversed with artificial ventilation in most cases (unpublished observation), i.e., the pattern is similar to pulmonary blood flow variation during the respiratory cycle (Baxter and Pearce, 1951; Brecher and Hubay, 1955; Barer and Nüsser, 1957; Franklin *et al.*, 1962; Hoffman *et al.*, 1965; Morgan *et al.*, 1966a and b; Charlier, 1967). Therefore this combination of varying pulmonary flow and mixed venous $P_{O_2}$ during the respiratory cycle as measured in the main pulmonary artery might tend to attenuate their effects but they are transmitted with different speed, i.e., flow variation by volume flow and $P_{O_2}$ by flow velocity, so that the mutual influence of these variations on oxygen uptake is difficult to predict.

Therefore we estimated the influence of variable oxygen uptake on $P_{Ae}O_2$ neglecting the true situation and only assuming that oxygen uptake varies sinusoidally in four different phase relationships with an ampitude of $\pm$ 10 %, $\pm$ 25 %, or $\pm$ 50 % of its mean value. The resulting $\Delta P_{Ae}O_2$ changed by up to $\pm$ 5 %, $\pm$ 12 % and $\pm$ 26 %, and $\overline{P_{Ae}O_2}$ by up to $\pm$ 0.3 mm Hg, $\pm$ 0.7 mm Hg, and $\pm$ 1.5 mm Hg, respectively, from the fixed oxygen uptake curves. Figure 7 shows the case of a $\pm$ 50 % variation

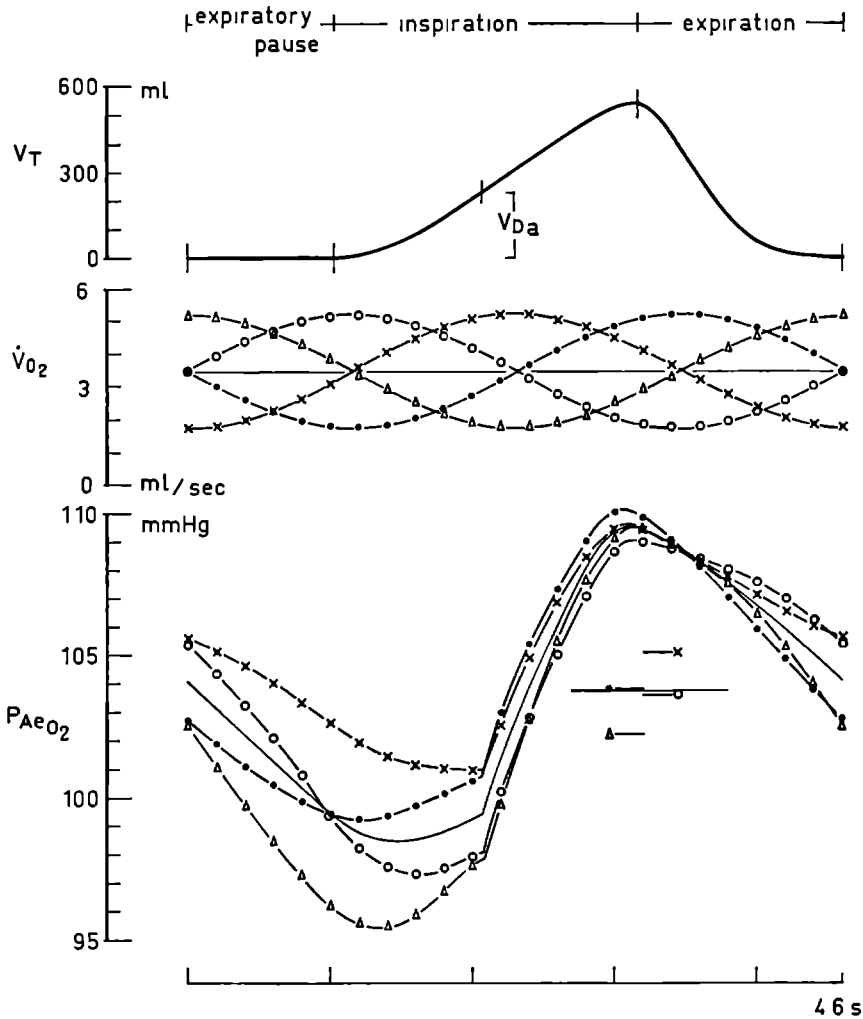



Fig 7 Influence of varying oxygen uptake ($\dot{V}_{O_2}$) on effective alveolar $P_{O_2}$ ($P_{Ae_{O_2}}$) Oxygen uptake was assumed to change in a sinusoidal curve with an amplitude of $\pm$ 50% of average $V_{O_2}$ Four different phase relationships to respiration are illustrated Curves are from top to bottom spirogram, varying oxygen uptake, effective alveolar $P_{O_2}$ Related oxygen uptake and $P_{Ae_{O_2}}$ are shown by the same respective symbols Short horizontal bars below the peaks of $P_{Ae_{O_2}}$ indicate respective mean values of $P_{Ae_{O_2}}$ Long bar is that of $P_{Ae_{O_2}}$ with fixed $V_{O_2}$ $V_{Da}$ = anatomical dead space

of oxygen uptake. $\Delta P_{Ae_{O_2}}$ was decreased and $\overline{P_{Ae_{O_2}}}$ was higher when oxygen uptake reached its maximum midway during inspiration (crosses in figure 7), and vice versa. When oxygen uptake changed concomitant with respiration, i e., increased during inspiration and decreased during expiration (full circles), or in reversed direction (phase shift of 180°, empty circles), the influence on $P_{Ae_{O_2}}$ was small These results agree with those of Suwa and Bendixen (1972) If we consider a $\pm$ 25 % variation of

oxygen uptake as the maximum value in the artificially ventilated dog according to the findings concerning pulmonary arterial flow by Charlier (1967) these deviations would be only $\pm$ 12 % in $\Delta P_{AeO_2}$ and $\pm$ 0.7 mm Hg in $\overline{P_{AeO_2}}$ from those with fixed oxygen uptake. In spite of these restrictions a highly significant correlation between $\Delta P_{AeO_2}$ and the amplitude of arterial oxygen fluctuation synchronous with respiration was found as reported in a companion paper (Yokota and Kreuzer, 1973).

## References


Barer, G. R. and E. Nüsser (1957). Pulmonary blood flow in the cat. The effect of positive pressure respiration. *J. Physiol.* (London) 138: 103–118.

Bartels, J., J. W. Severinghaus, R. E. Forster, W. A. Briscoe, and D. V. Bates (1954). The respiratory dead space measured by single breath analysis of oxygen, carbon dioxide, nitrogen or helium. *J. Clin. Invest.* 33: 41–48.

Baxter, I. G. and J. W. Pearce (1951). Simultaneous measurement of pulmonary arterial flow and pressure using condenser manometers. *J. Physiol.* (London) 115: 410–429.

Brecher, G. A. and C. A. Hubay (1955). Pulmonary blood flow and venous return during spontaneous respiration. *Circulation Res.* 3: 210–214.

Charlier, A. A. (1967). Beat to beat hemodynamic effects of lung inflation and normal respiration in anaesthetized and conscious dogs. Thesis, Louvain.

Chilton, A. B. and R. W. Stacy (1952). A mathematical analysis of carbon dioxide respiration in man. *Bull. Math. Biophys.* 14: 1–18.

Chilton, A. B., D. S. Barth, and R. W. Stacy (1954). A mathematical analysis of oxygen respiration in man. *Bull. Math. Biophys.* 16: 1–14.

Cumming, G. and K. H. Lin (1971). A model of time-varying gas exchange in the human lung during a respiratory cycle at rest. *Scand. J. Resp. Disease, Suppl.* 77: 34.

DuBois, A. B., A. G. Britt, and W. O. Fenn (1952). Alveolar $CO_2$ during the respiratory cycle. *J. Appl. Physiol.* 4: 535–548.

DuBois, A. B. and R. Marshall (1957). Measurements of pulmonary capillary blood flow and gas exchange throughout the respiratory cycle in man. *J. Clin. Invest.* 36: 1566–1571.

Ferris, E. B., G. L. Engel, C. D. Stevens, and J. Webb (1946). Voluntary breathholding. III. The relation of the maximum time of breathholding to the oxygen and carbon dioxide tensions of arterial blood, with a note on its clinical and physiological significance. *J. Clin. Invest.* 25: 734–743.

Fowler, W. S. (1948). Lung function studies. II. The respiratory dead space. *Am. J. Physiol.* 154: 405–416.

Franklin, D. L., R. L. van Citters, and R. F. Rushmer (1962). Balance between right and left ventricular output. *Circulation Res.* 10: 17–26.

Hoffman, J. I. E., A. Guz, A. A. Charlier, and D. E. L. Wilcken (1965). Stroke volume in conscious dogs; effect of respiration, posture, and vascular occlusion. *J. Appl. Physiol.* 20: 865–877.

Hughes, J. M. B., J. B. Glazier, J. E. Maloney, and J. B. West (1968a). Effect of lung volume on the distribution of pulmonary blood flow in man. *Respir. Physiol.* 4: 58–72.

Hughes, J. M. B., J. B. Glazier, J. E. Maloney, and J. B. West (1968b). Effect of extra-alveolar vessels on distribution of blood flow in the dog lung. *J. Appl. Physiol.* 25: 701–712.

Kelman, G. R. and J. F. Nunn (1966). Nomograms for correction of blood $P_{O_2}$, $P_{CO_2}$, pH, and base excess for time and temperature. *J. Appl. Physiol.* 21: 1484–1490.

Kimmich, H. P. and F. Kreuzer (1969). Catheter $P_{O_2}$ electrode with low flow dependency and fast response. In: Oxygen Pressure Recording in Gases, Fluids, and Tissues, edited by F. Kreuzer, Progr. in Resp. Res., Vol. 3, edited by H. Herzog, Karger, Basel, pp. 100–110.

Knelson, J H, W F Howatt, and G R Demuth (1970) Effect of respiratory pattern on alveolar gas exchange *J Appl Physiol* 29 328–331

Lamb, T W, N R Anthonisen, and S M Tenney (1965) Controlled frequency breathing during muscular exercise *J Appl Physiol* 20 244–248

Levy, S E, M Stein, R S Totten, I Bruderman, S W Wessler, and E D Robin (1965) Ventilation-perfusion abnormalities in experimental pulmonary embolism *J Clin Invest* 44 1699–1707

Morgan, B C, F L Abel, G L Mullins, and W G Guntheroth (1966a) Flow patterns in cavae, pulmonary artery, pulmonary vein, and aorta in intact dogs *Am J Physiol* 210 903–909

Morgan, B C, W E Martin, T F Hornbein, E W Crawford, and W G Guntheroth (1966b) Hemodynamic effects of intermittent positive pressure respiration *Anesthesiology* 27 584–590

Norris, R M (1967) The effect of breath holding on anatomical dead space in man *Clin Sci* 33 549–557

Nye, R E, Jr (1970) Influence of the cyclical pattern of ventilatory flow on pulmonary gas exchange *Respir Physiol* 10 321–337

Otis, A B, H Rahn, and W O Fenn (1948) Alveolar gas changes during breath holding *Am J Physiol* 152 674–686

Otis, A B (1964) Quantitative relationships in steady-state gas exchange In Handbook of Physiology Section 3 Respiration, Vol I, edited by W O Fenn and H Rahn, Washington, D C, American Physiological Society, pp 681–698

Pain, M C F and J B West (1966) Effect of the volume history of the isolated lung on distribution of blood flow *J Appl Physiol* 21 1545–1550

Riley, R L and A Cournand (1949) 'Ideal' alveolar air and the analysis of ventilation-perfusion relationships in the lungs *J Appl Physiol* 1 825–847

Ross, B B and L E Farhi (1960) Dead-space ventilation as a determinant in the ventilation-perfusion concept *J Appl Physiol* 15 363–371

Schuler, R and F Kreuzer (1967) Rapid polarographic in vivo oxygen catheter electrodes *Respir Physiol* 3 90–110

Severinghaus, J W and M Stupfel (1957) Alveolar dead space as an index of distribution of blood flow in pulmonary capillaries *J Appl Physiol* 10 335–348

Shepard, R H, E J M Campbell, H B Martin, and T Enns (1957) Factors affecting the pulmonary dead space as determined by single breath analysis *J Appl Physiol* 11 241–244

Snedecor, G W and W G Cochran (1968) Statistical methods Ames, Iowa, The Iowa State University Press pp 91–119

Stacy, R W and G H Kydd, III (1950) Variation of respiratory quotient during normal and deep exhalation *Federation Proc* 9 120–121

Strieder, D J, B A Barnes, B W Levine, and H Kazemi (1970) Stratified dead space in excised perfused lungs *J Appl Physiol* 29 486–492

Suwa, K and H H Bendixen (1972) Pulmonary gas exchange in a tidally ventilated single alveolus model *J Appl Physiol* 32 834–841

Vermeire, P and J Butler (1965) Changes of human pulmonary capillary blood flow due to respiration *Clin Res* 13 112

Workman, J M, R W B Penman, B Bromberger-Barnea, S Permutt, and R L Riley (1965) Alveolar dead space, alveolar shunt, and transpulmonary pressure *J Appl Physiol* 20 816–824

Yamamoto, W S (1960) Mathematical analysis of the time course of alveolar $CO_2$ *J Appl Physiol* 15 215–219

Yokota, H and F Kreuzer (1972) Respiratory fluctuations of oxygen tension in central venous blood of anesthetized dogs *Respir Physiol* 15 350–364

Yokota, H and F Kreuzer (1973) Alveolar to arterial transmission of oxygen fluctuations due to respiration in anesthetized dogs *Pflugers Arch* in press

# *Chapter II*

## ALVEOLAR TO ARTERIAL TRANSMISSION OF OXYGEN FLUCTUATIONS DUE TO RESPIRATION IN ANESTHETIZED DOGS*

**Abstract.** The amplitudes of respiratory oxygen fluctuations in the alveoli obtained by calculation were compared with those of the arterial blood measured by a catheter $P_{O_2}$ electrode in vivo in anesthetized and artificially ventilated dogs. It is shown that there is a significant correlation between them in general in both $P_{O_2}$ and $S_{O_2}$ though the latter correlates better. Amplitude ratio of arterial to alveolar $O_2$ fluctuations was calculated from two factors, i.e., dispersion of circulation time in the pulmonary vein and mixing in the left heart. The results of calculation agree satisfactorily with those obtained experimentally. The reduction of the amplitude of respiratory fluctuations of oxygen seems to be quite small in the aorta.

Oxygen fluctuations (respiratory)
Alveolar to arterial indicator transmission
Sympathomimetics
Artificial ventilation
Dog

After Chilton and Stacy (1952) as well as DuBois, Britt and Fenn (1952) reported a mathematical treatment of the cyclic variation of alveolar $CO_2$ due to the intermittent character of respiration, several reports dealt with this topic from different points of view (Chilton, Barth and Stacy, 1954; Yamamoto, 1960; Lamb, Anthonisen and Tenney, 1965; Nye, 1970; Cumming and Lin, 1971; Yokota, Hoofd and Kreuzer, 1973). On the other hand respiratory variations of arterial pH were demonstrated as early as in 1938 by Nims and Marshall, and later by Bjurstedt (1946), Åström (1952), and Honda and Ueda (1961); the last authors calculated arterial $P_{CO_2}$ variations from those of pH by the Henderson-Hasselbalch equation. Recently Band, Cameron and Semple (1969a and b) again showed the relationship of arterial pH variations with respiration.

Cyclic variations of arterial oxygen saturation with respiration were recorded already by Bjurstedt (1946) though the author did not comment on them. A purposeful exploration of this problem was performed by Bergman (1961) and Namur *et al.* (1961) by oximetry, and by Purves (1966) and Yokota and Kreuzer (1970) with polarographic oxygen electrodes. It is generally believed that the arterial fluctuations of $P_{O_2}$ and pH reflect the variations of the alveolar gases during the respiratory cycle although this relationship has not been studied quantitatively. Therefore we investigated the relationship between the respiratory fluctuations of $P_{O_2}$ in the alveoli and

* *Pflügers Archiv (1973), in press.*

those in the arterial blood, calculating the time course of alveolar $P_{O_2}$ ($P_{A_{O_2}}$) in steps of 0.2 sec as described in a previous paper (Yokota, Hoofd and Kreuzer, 1973) and measuring arterial $P_{O_2}$ ($P_{a_{O_2}}$) by a $P_{O_2}$ electrode developed in our laboratory (Kimmich and Kreuzer, 1969), also during sympathomimetic-induced changes of respiratory conditions with constant ventilation. The sympathomimetic drugs noradrenaline, adrenaline, isoprenaline, and TH1165a (hydroxyphenyl derivative of orciprenaline, Boehringer) were used because of their different actions in terms of predominant stimulation of α receptors, α and β receptors, β receptors, or $\beta_1$ activity, respectively. All of these agents induce bronchodilatation and enhance metabolism (Aviado, 1965; Engelhardt, 1964); adrenaline and isoprenaline are reported to influence physiological dead space and distribution of ventilation-perfusion ratio (Severinghaus and Stupfel, 1957; Hughes *et al.*, 1968); therefore they might directly influence pulmonary gas exchange even under fixed ventilation and change the time course of alveolar oxygen pressure (Yokota, Hoofd and Kreuzer, 1973). On the other hand they also act on the cardiovascular system and create different conditions for the transmission of alveolar oxygen variation to the blood in the aorta by changing cardiac frequency, blood flow, blood pressure, or vascular resistance.

In order to investigate the quantitative relationship between alveolar and arterial oxygen fluctuations we estimated the attenuation of respiratory fluctuation of $P_{O_2}$ during transmission from the alveoli to the aorta by the indicator dilution theory, using the time course of calculated alveolar $P_{O_2}$ as the input function. We found a significant correlation in the respiratory fluctuations of alveolar and arterial oxygen, both in terms of saturation and $P_{O_2}$, and good agreement between the estimated amplitude of respiratory fluctuation in arterial $P_{O_2}$ as obtained from that of alveolar $P_{O_2}$ and the observed arterial $P_{O_2}$ fluctuation.

## Methods

15 adult dogs, weighing 12 to 23 kg, were anesthetized with chloralose-urethane (for induction 25–50 mg/kg and 125–250 mg/kg, and for maintenance 5–10 mg/kg/h and 25–50 mg/kg/h, respectively) after premedication with acepromazine 1 mg/kg. The animal was loosely fixed in supine position and ventilated by a Harvard pump (model 607) through a cuffed tracheal tube, the ventilatory volume being adjusted to obtain about 4 % endtidal $CO_2$ at the beginning of the experiment; breathing frequency ranged from 12 to 18/min and this ventilation was maintained throughout the experiment. Spontaneous breathing was suppressed by continuous infusion of diallylnortoxiferine (Alloferin, Roche), 6 mg/kg/h, in saline (1 ml/min).

Respiratory flow was recorded by a pneumotachograph and respiratory $P_{O_2}$ and $P_{CO_2}$ were monitored by a catheter $P_{O_2}$ electrode (Schuler and Kreuzer, 1967) and an infrared $CO_2$ analyzer, respectively. Arterial and mixed venous $P_{O_2}$ were measured continuously in the proximal descending aorta and in the pulmonary artery, respectively, by blood-type catheter $P_{O_2}$ electrodes (Kimmich and Kreuzer, 1969) introduced from the femoral vessels, in order to have an idea of blood gas changes

during the various procedures applied (see below). Hollow catheters positioned in the same place as the $P_{O_2}$ electrodes were used for blood sampling and pressure recording (Statham strain gauge). Another hollow catheter was placed just below the veno-atrial junction through a cubital vein for infusion of muscle relaxant and sympathomimetics. All catheterizations were conducted under fluoroscopic guidance. Blood clotting was prevented by intravenous heparin administration (2 ml of heparin solution containing 5000 units/ml at the beginning and 3 to 4 hours later or when some clotting was seen in sampled blood). Pneumotachogram, respiratory $P_{O_2}$ and $P_{CO_2}$, arterial and mixed venous $P_{O_2}$, and arterial and venous pressures were recorded by a Honeywell Visicorder 1108.

After 2 sets of control samples, consisting of simultaneous arterial and mixed venous blood and expiratory gas, the dog received a continuous infusion of a sympathomimetic (adrenaline 5 μg/kg/min, noradrenaline 5 μg/kg/min, isoprenaline 1 μg/kg/min, or TH1165a 0.5 μg/kg/min) for 45 to 60 min. During sympathomimetic infusion blood and gas samples were collected about every 15 min and the last samples were taken 15 to 20 min after the end of infusion. Subsequently the dog received isotonic bicarbonate solution to readjust the pH lowered by the sympathomimetic to the normal range before the subsequent infusion of a sympathomimetic. At the end of the experiment the animal was ventilated with a hypoxic gas mixture to get calibration points for the blood and gas $P_{O_2}$ electrodes.

Blood samples were analyzed instantaneously for $P_{O_2}$, $P_{CO_2}$, and pH by a Radiometer Gasmonitor (type PHA 927b, Copenhagen) and a Radiometer pH meter (type PHM 22r), respectively. When the body temperature of the dog, measured deep in the rectum by a mercury thermometer, differed from that of the instruments, blood gas pressures and pH were corrected according to Kelman and Nunn (1966). Expired gas samples collected in an anesthesia bag were analyzed for $CO_2$ and $O_2$ by an infrared analyzer and a paramagnetic oxygen analyzer, respectively. Arterial and capillary oxygen saturations were calculated from arterial and alveolar $P_{O_2}$, arterial pH and body temperature according to Rossing and Cain (1966), assuming that end-capillary $P_{O_2}$ is in equilibrium with alveolar $P_{O_2}$. Effective alveolar $P_{O_2}$ ($P_{Ae_{O_2}}$) was calculated as explained in the preceding report (Yokota, Hoofd and Kreuzer, 1973) during each sampling period every 0.2 sec throughout the respiratory cycle from FRC, tidal volume, respiratory flow, oxygen uptake, respiratory exchange ratio, mean expiratory $P_{CO_2}$, endtidal $P_{CO_2}$, and arterial $P_{CO_2}$. FRC was measured by the open nitrogen method after the first infusion run and assumed to remain unchanged during the experiment.

The statistical significance of the differences in the amplitude ratio of respiratory oxygen fluctuation in the lung and in the aorta was assessed by Student's t test between groups with different sympathomimetics and between control values and those during sympathomimetic infusion in each group. Significance of correlation between the amplitudes of oxygen fluctuation in the lung and in the aorta and between the amplitude ratio and the time of the ventilatory cycle was evaluated by the test of r following Snedecor and Cochran (1968). The limit of significance was assumed at $p = 0.05$.

## Results

Figure 1 is part of a record of an experiment including calculated $P_{AeO_2}$. $P_{AeO_2}$ and $P_{aO_2}$ show fluctuations with the same period as ventilation, a pattern seen in all cases. The time lag between the fluctuations of $P_{AeO_2}$ and $P_{aO_2}$ (horizontal distance between b and c in figure 1) is due to the circulation time from the lung capillaries to the proximal descending aorta which varies during the experiment from time to time and from dog to dog, ranging from 1.4 to 5 sec as measured, for convenience of reading, from the ascending limb of respiratory $P_{O_2}$ as a reference point to the lowest point of

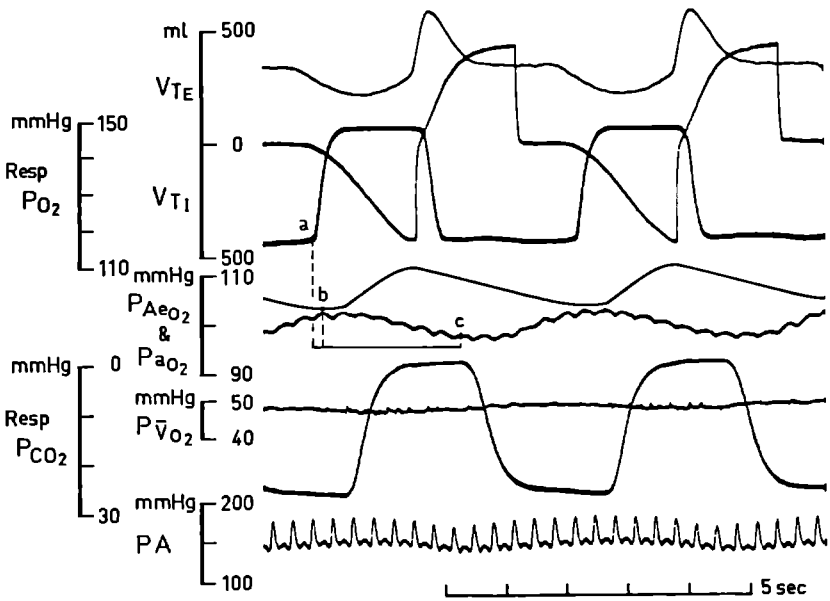



Fig. 1. Record showing that respiratory fluctuations of arterial oxygen tension ($P_{aO_2}$), measured by a catheter $P_{O_2}$ electrode in the proximal descending aorta, have the same period as other respiratory parameters, particularly also alveolar oxygen tension ($P_{AeO_2}$). Tracings from top to bottom: pneumotachogram, tidal volume (inspiratory = $V_{TI}$, expiratory = $V_{TE}$), respiratory $P_{O_2}$ (Resp $P_{O_2}$), effective alveolar $P_{O_2}$ ($P_{AeO_2}$), arterial $P_{O_2}$ ($P_{aO_2}$), respiratory $P_{CO_2}$ (Resp $P_{CO_2}$), mixed venous $P_{O_2}$ ($P\bar{v}_{O_2}$), and arterial blood pressure (PA).

$P_{aO_2}$ (from point a to c in figure 1; gas-type $P_{O_2}$ electrode placed just below the pneumotachographic head). Actually this involves a minor overestimation of the circulation time (between a and b in figure 1) because the lowest point of $P_{AeO_2}$ occurs somewhere during reinspiration of antomical dead space gas as depending on various factors. The amplitude of $P_{AeO_2}$ and $P_{aO_2}$ (the amplitude is the vertical distance from peak to bottom of the respiratory fluctuations) increased during sympathomimetic infusion.

Figure 2 shows the amplitudes of $P_{AeO_2}$ fluctuation ($\Delta P_{AeO_2}$) plotted on the abscis-

sa and those of $Pa_{O_2}$ ($\Delta Pa_{O_2}$) on the ordinate for all experiments. There is a significant correlation between $\Delta PAe_{O_2}$ and $\Delta Pa_{O_2}$ on the average ($\Delta Pa_{O_2} = 0.304\ \Delta PAe_{O_2} + 1.167$; $p < 0.001$). The groups of dots connected by solid lines show the change of $\Delta P_{O_2}$ in the alveoli and in the arterial blood in each individual infusion run.

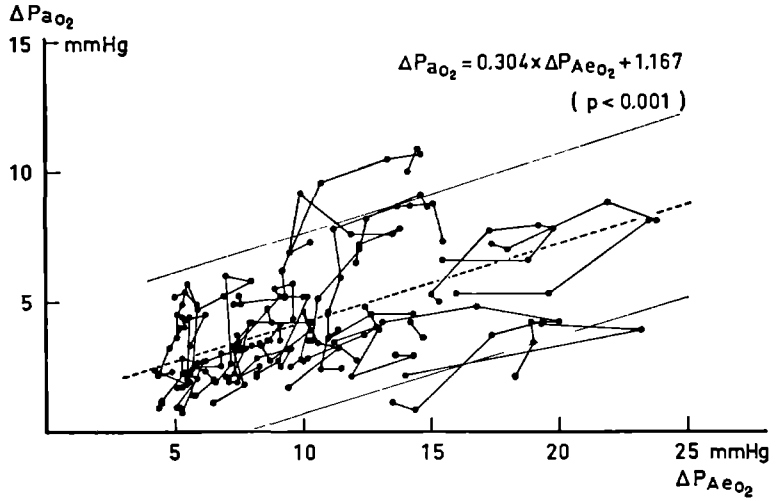



Fig. 2. Relationship between the amplitudes of respiratory fluctuations of effective alveolar $P_{O_2}$ ($\Delta PAe_{O_2}$) and arterial $P_{O_2}$ ($\Delta Pa_{O_2}$). Groups of dots connected by solid lines show changes of $\Delta PAe_{O_2}$ and $\Delta Pa_{O_2}$ during individual runs of sympathomimetic infusion. Broken line shows regression line (formula in upper right of figure); thin parallel lines show 95% confidence limit.

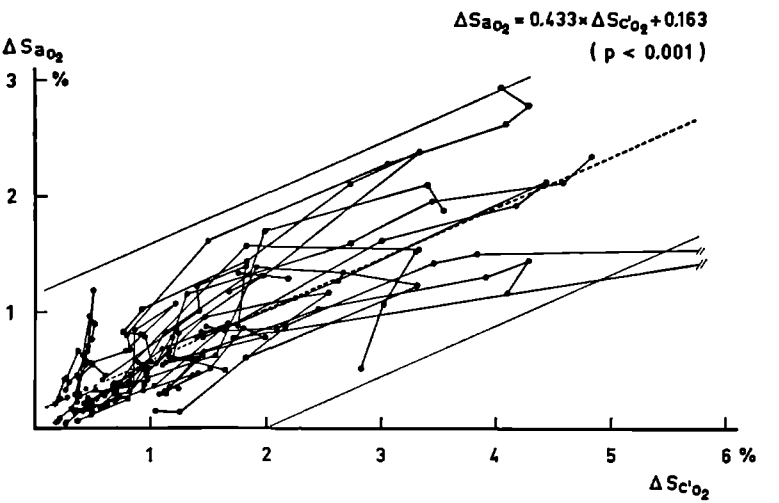



Fig. 3. Relationship between the amplitudes of respiratory fluctuations of endcapillary oxygen saturation ($\Delta Sc'_{O_2}$) and arterial oxygen saturation ($\Delta Sa_{O_2}$). Regression line is shown by broken line (formula in upper right of figure); thin parallel lines are 95% confidence limits. Note that groups of dots connected by solid lines, showing changes of $\Delta Sc'_{O_2}$ and $\Delta Sa_{O_2}$ during individual infusion runs, are more parallel to regression line than in figure 2.

When the same values were compared in terms of saturation, the correlation between the variations of $O_2$ fluctuation in the alveoli (or in the endcapillaries in terms of saturation) and in the arterial blood during each infusion was much better and all experiments (except two runs) showed a significant correlation. Figure 3 illustrates the relationship between the amplitudes of respiratory fluctuation of endcapillary and arterial oxygen saturation ($\Delta Sc'_{O_2}$ and $\Delta Sa_{O_2}$, respectively). The regression line (interrupted line) is highly significant ($\Delta Sa_{O_2} = 0.434\ \Delta Sc'_{O_2} + 0.163$; $p < 0.001$) and, as shown in the figure, the change of $\Delta S_{O_2}$ during each individual infusion (dots connected by solid line) is more consistent with the regression line than concerning $\Delta P_{O_2}$ in figure 2.

The ratios of the amplitudes of respiratory fluctuation of oxygen in the arterial blood to those in the alveoli or in the endcapillaries, both in terms of $P_{O_2}$ and $S_{O_2}$, did not show any significant difference between control values and those during infusion in each group with the same sympathomimetic or between groups with different sympathomimetics.

Considering the transport of $O_2$ in terms of an indicator dilution process we have calculated the amplitude ratio of alveolar fluctuation of $O_2$ resulting from damping by two factors, i.e., mixing in the left heart and dispersion of circulation time. $P_{AeO_2}$ was used as input function for the calculation because the dissociation curve of $O_2$ may be regarded as almost straight at the alveolar $P_{O_2}$ of normoxia. The amplitude ratio before and after mixing in the left heart was examined at assumed heart rates of 300/min, 200/min, and 100/min on 15 $P_{AeO_2}$ curves chosen arbitrarily in each dog for various endsystolic to enddiastolic volume ratios ($Q_{es}/Q_{ed}$)as described below. When assuming complete mixing in the ventricle the concentration after dilution is:

$$C_m = k \,.\, C_{m-1} + (1 - k)\, I_m \qquad (1)$$

where $C_m$ and $C_{m-1}$ are the output $O_2$ concentrations at the m-th and (m — 1)th beat, respectively, $I_m$ is the input $O_2$ concentration between the m-th and (m — 1)th beat, and $k = Q_{es}/Q_{ed}$.

Figure 4 shows the results of the computed attenuation of the amplitude due to the mixing chamber. The attenuation of the amplitude is plotted on the ordinate and the breathing frequency to cardiac frequency ratio ($f_v/f_c$) on the abscissa for four values of $Q_{es}/Q_{ed}$. The ratio $f_v/f_c$ was chosen because the attenuation due to the mixing chamber depended on the number of heart beats per breath and not on the absolute value of breathing or cardiac frequency. Thus there would be no attenuation of the amplitude if $f_v/f_c = 0$, and the amplitude would be completely damped out if $f_v/f_c = 1$. Our calculation did not cover the whole range of $f_v/f_c$ from 0 to 1, but only from 0.04 to 0.183 with breathing frequencies as used and cardiac frequencies assumed. Four values of $Q_{es}/Q_{ed}$, 0.4, 0.57, 0.6, and 0.66, were chosen from the reports of Bartle and Sanmarco (1966) as obtained in dogs by angiocardiographic technique, of Holt (1966) in various species of animals by indicator wash-out method, and of Bristow *et al.* (1963) in chloralose-anesthetized dogs with and without isoprenaline infusion by in-

dicator wash-out technique, respectively Curves through plots for various $Q_{es}/Q_{ed}$ were fitted by eye. Since ventilation was fixed in our experiments either increase of cardiac frequency or decrease of $Q_{es}/Q_{ed}$ augments the amplitude ratio, i e , diminishes attenuation.

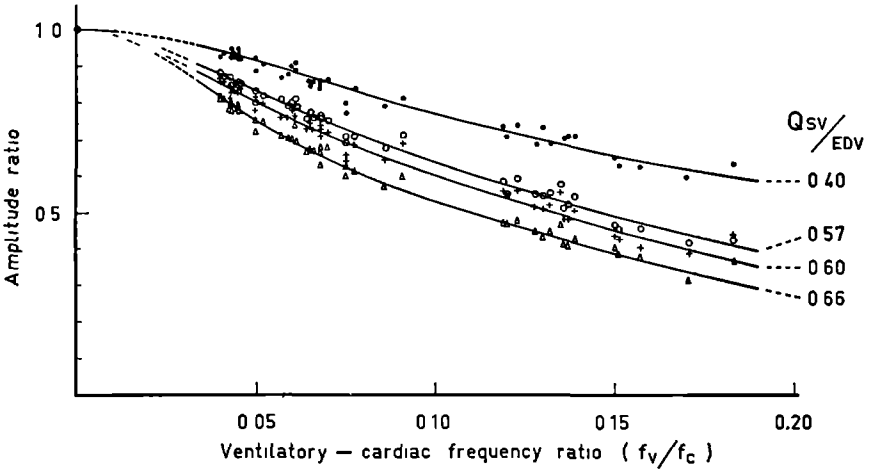



Fig 4 Relationship between amplitude ratio of respiratory fluctuations of oxygen before and after passing the mixing chamber of the left heart and ventilatory to cardiac frequency ratio Curves were fitted by eye to plots for four values of endsytolic to enddiastolic volume ratio ($Q_{es}/Q_{ed}$), taken (from top to bottom) from the reports of Bartle and Sanmarco (1966) measured in dogs by angiocardiographic method (0 4), of Holt (1966) in various species of animals by indicator washout technique (0 57), and of Bristow et al (1963) in chloralose-urethane anesthetized dogs with and without isoprenaline infusion measured by indicator washout method (0 6 and 0 66)

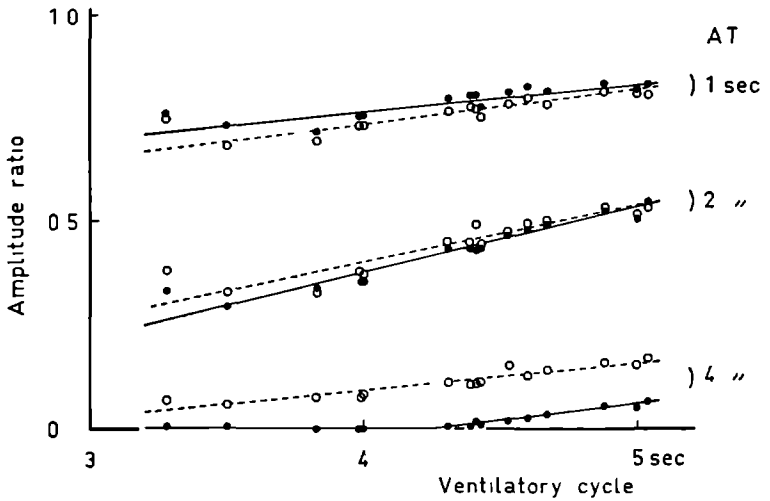



Fig 5 Effect of dispersion of circulatory time on transmission of respiratory fluctuations of oxygen. Amplitude ratio before and after passing a distance corresponding to appearance time (AT) changes with ventilatory frequency Dots and solid lines show results from isosceles triangle function, circles and broken lines those from gamma function

Attenuation due to dispersion of circulation time was calculated assuming that the distribution frequency of circulation time is given by an isosceles triangle (Allen and Taylor, 1924) or by a gamma function (Thompson *et al.*, 1964) and that mean circulation time is twice the appearance time according to Zierler (1962), Knopp and Bassingthwaighte (1969), and Shaffer *et al.* (1971), using the formula of Zierler (1962) for continuous input of indicator. The constant for the gamma function was assumed to have a value of 0.52 for the ratio of appearance-to-half way peak time/appearance-to-peak time according to Thompson *et al.* (1964).

Figure 5 shows the results with assumed appearance times of 1, 2, and 4 sec on 15 curves of $P_{Ae}O_2$ as used for calculation of the mixing chamber amplitude ratio. There was no clear-cut difference in amplitude ratio between isosceles triangle (full circles) and gamma function (open circles) with short circulation times; with 4 sec appearance time the amplitude ratio with the isosceles triangle was nearly zero whereas with the gamma function there was still some remaining fluctuation to be expected in the arterial blood. Whatever frequency function and appearance time are, there is a constant tendency that increase of breathing frequency is accompanied by a decrease of the amplitude ratio ($p < 0.01$ in all cases except for the isosceles triangle method at 4 sec appearance time), particularly at an appearance time of 2 sec. Since the total transfer function over several compartments is the product of the individual transfer functions, the amplitude ratio of arterial $O_2$ fluctuation to that in the alveoli or in the endcapillaries could be obtained from figures 4 and 5. When taking the mean breathing frequency of the experiments as 13.9/min, cardiac frequency as 120/min to 180/min, $Q_{es}/Q_{ed}$ as 0.4 and 0.66, and appearance time as 1 sec, we get 0.64 to 0.56 and 0.47 to 0.36 for the smaller and larger values of $Q_{es}/Q_{ed}$, respectively, for the total amplitude ratio from lung to aorta.

## Discussion

Arterial $O_2$ fluctuations with the same frequency as respiration were reported by several authors and interpreted as a reflection of alveolar $O_2$ variation during the respiratory cycle. In the present study we observed the same phenomenon in all cases. Possibilities of artefacts from the blood-type catheter $P_{O_2}$ electrode used in this study could be excluded. The flow artefact, which increases above 2 % of total deflection with flows of less than 5 cm/sec, was negligible because simultaneous flow measurement within 1 or 2 cm from the $P_{O_2}$ electrode by an electromagnetic catheter tip flowmeter (Trasflow 600, Skalar, Delft) did not show any consistent relationship between change of $Pa_{O_2}$ and instantaneous flow variation during the respiratory cycle. Blood pressure does not influence the $P_{O_2}$ electrode as shown in figure 6, where in the left half the tracings of two $P_{O_2}$ electrodes at the same place in the proximal descending aorta were completely superimposed whereas in the right half they were separated by 30 cm causing a time delay of 0.7 to 0.8 sec between them, corresponding to the mean flow velocity. Since on the other hand the pressure wave is transmitted much faster than mean flow velocity, artefacts due to pressure can be excluded. Respiratory

temperature variation in arterial blood as reported by Wessel, James and Paul (1966) is too small to cause any noticeable change in $P_{O_2}$. Small oscillations of $P_{O_2}$ with the same frequency as heart beat are superimposed on the respiratory fluctuations. The same phenomenon was observed by Purves (1966) who explained it physiologically whereas Band, Cameron and Semple (1969a) attributed this type of oscillations in arterial pH to an artefact. The response time of the $P_{O_2}$ electrode (0.4 sec for 95 % deflection), however, is not quite short enough to follow cardiac oscillations of $P_{O_2}$ with a rate of about 150/min faithfully.

If the $Pa_{O_2}$ fluctuations with the same frequency as respiration are a reflection of the respiratory $P_{AO_2}$ changes, their respective deflections must be related as shown for both $\Delta S_{O_2}$ and $\Delta P_{O_2}$ in the present study. The poorer relationship in $\Delta P_{O_2}$ may be understood from the shape of the $O_2$ dissociation curve, the existence of an alveolar-arterial $O_2$ gradient, and the shift of the dissociation curve due to pH change during sympathomimetic infusion (decrease of pH from 7.404 $\pm$ 0.040 S.D. in the control period to 7.245 $\pm$ 0.052 S.D. in the last samples during infusion; $p < 0.005$, $n = 26$).

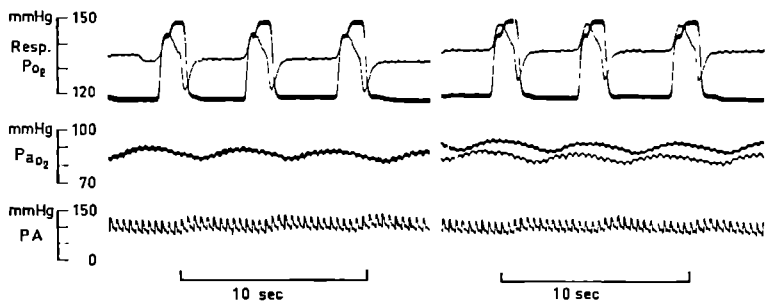



Fig. 6. Recording of respiratory fluctuations of arterial $P_{O_2}$ ($Pa_{O_2}$) with two catheter $P_{O_2}$ electrodes in the aorta of a dog breathing spontaneously. Tracings of both electrodes are almost completely superimposed in the left half when both were at the same location in the aorta; in the right half one of the electrodes was shifted downstream by 30 cm (upper tracing of $Pa_{O_2}$) and its tracing was displaced upward for better visibility.

All these three complications arising from the $O_2$ dissociation curve were absent when considering saturation as shown in figure 3 where a better correlation between $\Delta Sc'_{O_2}$ and $\Delta Sa_{O_2}$ is seen. It should be noted that both arterial and endcapillary saturation, and therefore $\Delta Sa_{O_2}$ and $\Delta Sc'_{O_2}$ were calculated with arterial pH, and not with the true pH in arterial and endcapillary blood, which is also subject to respiratory fluctuations as demonstrated by several investigators. If we assume that the fluctuation of alveolar $P_{CO_2}$ is as large as $\Delta PAe_{O_2}$ (mean = 10.1 $\pm$ 4.25 S.D. mm Hg, $n = 185$), the variation of endcapillary pH would be 0.1 pH unit according to the Henderson-Hasselbalch equation. It is interesting to note that the amplitude of respiratory variation of arterial pH given by Band, Cameron and Semple (1969a) is very close to the value expected from this and the amplitude ratio of $\Delta S_{O_2}$ (figure 3).

Calculation shows that, in the normal range of pH, $\Delta Sc'_{O_2}$ is underestimated by 50 % when taking one average pH value instead of a fluctuation of 0.1 pH unit and $\Delta Sa_{O_2}$ by about 40 % with one average pH value instead of 0.05 pH unit difference (assumed from figure 3 with 0.1 pH unit difference in the capillary). Therefore the line of the relationship of $\Delta S_{O_2}$ in figure 3 is possibly lowered by about 10 % when the true pH is applied. However, due to wide scatter of the points a variation of the slope by 10 % does not induce any significant shift in the regression line ($0.497 \geqslant \beta \geqslant 0.369$, $\beta = 95$ % limit of the slope).

Yamamoto (1962) calculated the effect of mixing on the amplitude ratio of respiratory variation of $CO_2$ considering left atrium and left ventricle. According to Brecher and Galletti (1962) as well as Murray, Kennedy and Figley (1968), however, the left atrium seems to be inferior to the ventricle as a mixing chamber. Therefore we neglected the effect of atrial mixing and considered only the ventricular effect with four assumed $Q_{es}/Q_{ed}$ values. The value of $Q_{es}/Q_{ed}$ has been a point of dispute between the studies using indicator wash-out methods and those with angiographic techniques, the latter giving 15 to 30 % smaller values. It is argued that wash-out methods are affected by incomplete mixing in the ventricle (Irisawa, Wilson and Rushmer, 1960; Swan and Beck, 1960; Bartle and Sanmarco, 1966; Maseri and Enson, 1968). A recent study using echocardiography by Pombo, Troy and Russell (1971) showed good agreement with angiocardiographic techniques. However, as we assumed complete mixing in the ventricle, it might be more reasonable to follow the indicator dilution techniques which were based on the same assumption as our calculation. Furthermore the term 'chamber' used here may not be confined to the ventricle but might also include the root of the aorta, since the same sort of wash-out curve is obtained by aortic root injection as by ventricular injection (Freis and Heath, 1964). Since, however, $Q_{es}/Q_{ed}$ varies from subject to subject and also with cardiac rate (Holt, 1956), the difference between indicator wash-out and angiographic values may not be so important.

Bristow *et al.* (1963) demonstrated a change of $Q_{es}/Q_{ed}$ with indicator wash-out technique under isoprenaline infusion. From figure 4 we expect an increase of the amplitude ratio by two factors, increase of cardiac rate under fixed ventilation as in our study (decrease of $f_v/f_c$) and decrease of $Q_{es}/Q_{ed}$. The third and fourth curves (from top) concern $Q_{es}/Q_{ed}$ during infusion of isoprenaline and control period, respectively (Bristow *et al.*, 1963). Figure 7 shows the change of $\Delta Pa_{O_2}$ at the start of isoprenaline infusion (1 µg/kg/min), involving changes of blood pressure, blood $P_{O_2}$, mixed venous temperature, and $P_{O_2}$ and $P_{CO_2}$ in expiratory gas; the amplitude ratio in $\Delta S_{O_2}$, calculated from control sample and just afterwards, changed from 0.49 to 0.71. Apart from the change of $Q_{es}/Q_{ed}$ and cardiac rate, a change of transit time due to alteration of cardiac output might be involved too. However, we could not find any significant difference of the amplitude ratios between control values and those during sympathomimetic infusion ($p > 0.05$).

The effect of another factor of damping in the transmission of $O_2$ fluctuations, the dispersion of circulation time from lung capillaries to left atrium, is shown in figure 5.

It might be expected that the amplitude ratio should be reduced markedly when measuring $\Delta$ $Pa_{O_2}$ in the distal part of the descending aorta instead of just below the arch and adding some time delay in appearance time, for example one sec as in figure 6. This anticipation, however, is not borne out since the pattern and the amplitude of $Pa_{O_2}$ fluctuation in the proximal and distal part of the aorta are almost

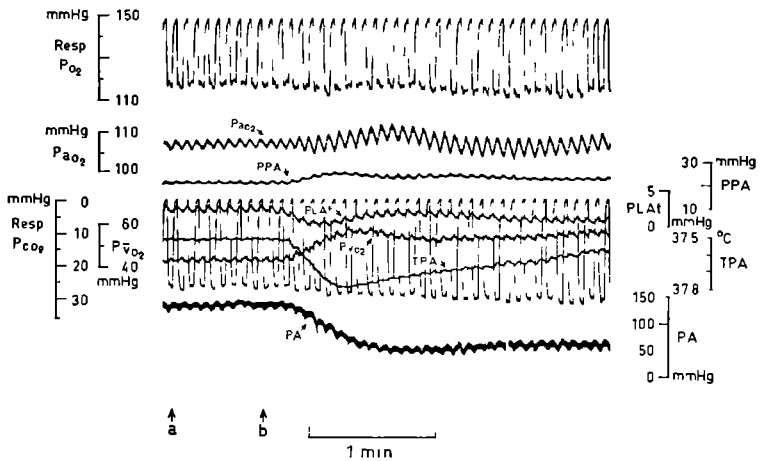



Fig. 7. Recording of an experiment at the beginning of isoprenaline infusion (1 µg/kg/min). Arrows a and b show start of the infusion pump and first change in the parameters (here left atrial pressure), respectively. Arterial $P_{O_2}$ ($Pa_{O_2}$), the second tracing from top, shows increased amplitude of respiratory fluctuations (amplitude doubled) while $\Delta$ $PAe_{O_2}$ changed from 7.4 mm Hg in the control period to 9.1 mm Hg after infusion. Other tracings from top to bottom are: respiratory $P_{O_2}$ (Resp. $P_{O_2}$), pulmonary arterial pressure (PPA), respiratory $P_{CO_2}$ (Resp. $P_{CO_2}$), left atrial pressure (PLAt), pulmonary arterial temperature (TPA), mixed venous $P_{O_2}$ ($P\bar{v}_{O_2}$), and arterial blood pressure (PA).

completely superimposable (figure 6). This discrepancy may be attributed to the characteristics of aortic flow which is flat or skewed in velocity profile in certain periods of the cardiac cycle, and disturbed in some cardiac phases but rarely turbulent (Ling *et al.*, 1968; Bergel *et al.*, 1970; Seed and Wood, 1971); this pattern would limit dispersion of circulation time as compared with the venous side of the lung. Bassingthwaighte and Ackerman (1967), on the other hand, reported a transfer function in the aortic flow of dogs having a ratio of appearance time/mean circulation time of nearly 0.5; in this case damping during passage through the aorta would be unavoidable. The reason for this contradiction is not clear but may be due to differences in indicator addition, in hemodynamics by different kinds of ventilation, or to exsanguination. At least as far as such a short-term sequence like respiratory fluctuation is concerned, a transfer function similar to that in the lung may not be extrapolated to the aortic side.

In preliminary experiments on 3 dogs we measured the appearance time from the pulmonary capillary, or more exactly the trachea, to the left atrium with a catheter

$P_{O_2}$ electrode introduced by the transseptal technique while changing inspiratory $O_2$ concentration. The mean value of 9 measurements was 1.2 sec $\pm$ 0.24 S.D. sec; when considering the time lag between trachea and alveoli in figure 1, about one sec results for the mean appearance time over this distance. This value seems reasonable since Shaffer *et al.* (1971) reported an appearance time across the lung, i.e., the pulmonary artery, the capillary, and the vein, of about 2 sec. Therefore the damping due to dispersion of circulation time in the pulmonary veins is likely to fall in the range of the top curves with an appearance time of 1 sec in figure 5.

Apart from the two factors for the attenuation of respiratory $O_2$ fluctuation mentioned above, the shunt ratio may play a role. Since the shunt ratio is a mixture of true shunt and distribution ratio which is influenced by perfusion pressure, transpulmonary pressure, lung volume, etc. (West, Dollery and Naimark, 1964; Anthonisen and Milic-Emili, 1966; Kaneko *et al.*, 1966; Pain and West, 1966; Dollfuss, Milic-Emili and Bates, 1967; Hughes *et al.*, 1968; Hogg *et al.*, 1971), it might also be expected to show a cyclic pattern with respiration. There are not enough data available, however, to take this factor into account.

The estimation of the amplitude ratio in respiratory $O_2$ fluctuation showed that the relationship between alveolar and arterial $O_2$ fluctuations agrees satisfactorily with theoretical evaluation. This agreement might be taken as evidence for the validity of the lung model and the $P_{Ae_{O_2}}$ calculation presented in the companion paper; the bearing of this model cannot be proven directly at this moment. Further support for our estimation of the attenuation ratio might be sought in the application of a foreign indicator dilution technique but not much could be expected from it. Conventional indicator dilution curves recorded on the arterial side (with injection on the venous side or in the lung) are much longer than a normal breathing cycle which would lead to underestimation of the effect of the mixing chamber or decrease of $f_v/f_c$ in figure 4 (concomitant with increase of amplitude ratio and therefore diminution of attenuation).

## References


Allen, C. M. and E. A. Taylor (1924). The salt velocity method of water measurement. *Mech. Engineering* 46: 13.

Anthonisen, N. R. and J. Milic-Emili (1966). Distribution of pulmonary perfusion in erect man. *J. Appl. Physiol.* 21: 760–766.

Åström, A. (1952). On the action of combined carbon dioxide excess and oxygen deficiency in the regulation of breathing. *Acta Physiol. Scand.* 27, *Suppl.* 98: 1–61.

Aviado, D. M. (1965). The lung circulation. Vol. I, Oxford, Pergamon Press, pp. 355–384.

Band, D. M., I. R. Cameron, and S. J. G. Semple (1969a). Oscillations in arterial pH with breathing in the cat. *J. Appl. Physiol.* 26: 261–267.

Band, D. M., I. R. Cameron, and S. J. G. Semple (1969b). Effect of different methods of $CO_2$ administration on oscillations of arterial pH in the cat. *J. Appl. Physiol.* 26: 268–273.

Bartle, S. H. and M. E. Sanmarco (1966). Comparison of angiocardiographic and thermal washout technics for left ventricular volume measurement. *Am. J. Cardiol.* 18: 235–252.

Bassingthwaighte, J. B. and F. H. Ackerman (1967). Mathematical linearity of circulatory transport. *J. Appl. Physiol.* 22: 879–888.

Bergel, D. H., C. Clark, D. L. Schultz, and D. S. Tunstall Pedoe (1970). The measurement of instantaneous blood velocity and a calculation of total mechanical energy expenditure in ventricular pumping In: Fluid Dynamics of Blood Circulation and Respiratory Flow AGARD Conference Proceedings No. 65. pp. 19/1–15.

Bergman, N A. (1961). Cyclic variations in blood oxygenation with the respiratory cycle. *Anesthesiology* 22: 900–908.

Bjurstedt, A. G. H. (1946). Interaction on centrogenic and chemoreflex control of breathing during oxygen deficiency at rest. *Acta Physiol. Scand 12, Suppl 38* 1–88.

Brecher, G. A. and P. M Galletti (1963). Functional anatomy of cardiac pumping. In: Handbook of Physiology. Section 2: Circulation. Vol. II, edited by W. F. Hamilton and P. Dow. Washington, D. C , American Physiological Society. pp. 759–798.

Bristow, J. D., R. E. Ferguson, F. Mintz, and E. Rapaport (1963). Thermodilution studies of ventricular volume changes due to isoproterenol and bleeding. *J. Appl Physiol* 18: 129–133.

Chilton, A. B. and R. W. Stacy (1952) A mathematical analysis of carbon dioxide respiration in man. *Bull Math. Biophys.* 14: 1–18.

Chilton, A B., D S. Barth, and R W. Stacy (1954) A mathematical analysis of oxygen respiration in man. *Bull. Math. Biophys.* 16: 1–14.

Cumming, G. and K. H. Lin (1971). A model of time-varying gas exchange in the human lung during a respiratory cycle at rest. *Scand. J. Respir Disease, Suppl.* 77: 34.

Dollfuss, R. E , J. Milic-Emili, and D. V. Bates (1967) Regional ventilation of the lung, studied with boluses of $^{133}$xenon. *Respir. Physiol.* 2: 234–246.

DuBois, A B., A. G. Britt, and W. O. Fenn (1952). Alveolar $CO_2$ during the respiratory cycle. *J. Appl. Physiol.* 4: 535–548.

Engelhardt, A. (1964). Pharmacology of the sympathomimetic broncholytic Th 1165. C. H. Boehringer Sohn, Ingelheim am Rhein.

Freis, E. D. and W. C. Heath (1964). Hydrodynamics of aortic blood flow. *Circulation Res* 14: 105–116.

Hogg, J. C., P. Holst, P. Corry, F. Ruff, E. Housley, and E. Morris (1971). Effect of regional lung expansion and body position on pulmonary perfusion in dogs. *J. Appl. Physiol.* 31: 97–101.

Holt, J. P. (1956) Estimation of the residual volume of the ventricle of the dog's heart by two indicator dilution technics *Circulation Res.* 4: 187–195.

Holt, J. P. (1966). Indicator-dilution methods: Indicators, injection, sampling and mixing problems in measurement of ventricular volume *Am. J. Cardiol* 18: 208–225.

Honda, Y. and M. Ueda (1961). Fluctuations of arterial pH associated with the respiratory cycle in dogs *Jap J. Physiol* 11: 223–228.

Hughes, J. M B , J B Glazier, J E. Maloney, and J. B West (1968) Effect of extra-alveolar vessels on distribution of blood flow in the dog lung. *J. Appl Physiol* 25: 701–712.

Irisawa, H , M. F. Wilson, and R. F. Rushmer (1960). Left ventricle as a mixing chamber. *Circulation Res.* 8: 183–187.

Kaneko, K , J. Milic-Emili, M B. Dolovich, A. Dawson, and D. V. Bates (1966). Regional distribution of ventilation and perfusion as a function of body position *J. Appl Physiol.* 21: 767–777.

Kelman, G. R. and J F. Nunn (1966). Nomograms for correction of blood $P_{O_2}$, $P_{CO_2}$, pH, and base excess for time and temperature *J Appl Physiol.* 21: 1484–1490

Kimmich, H. P and F. Kreuzer (1969) Catheter $P_{O_2}$ electrode with low flow dependency and fast response. In: Oxygen Pressure Recording in Gases, Fluids, and tissues, edited by F. Kreuzer, Progr. in Resp. Res., Vol. 3, edited by H Herzog Basel, Karger, pp. 100–110.

Knopp, T. J. and J. B. Bassingthwaighte (1969). Effect of flow on transpulmonary circulatory transport functions. *J. Appl. Physiol.* 27: 36–43.

Lamb, T. W., N. R. Anthonisen, and S. M Tenney (1965). Controlled frequency breathing during muscular exercise *J. Appl. Physiol.* 20: 244–248.

Ling, S. C , H. B. Atabek, D L. Fry, D. J. Patel, and J. S. Janicki (1968). Application of heated-film velocity and shear probes to hemodynamic studies. *Circulation Res.* 23: 789–801.

Maseri, A. and Y. Enson (1968). Mixing in the right ventricle and pulmonary artery in man: Evaluation of ventricular volume measurements from indicator washout curves. *J. Clin. Invest.* 47: 848–859.

Murray, J. A., J. W. Kennedy, and M. M. Figley (1968). Quantitative angiocardiography. II. The normal left atrial volume in man. *Circulation* 37: 800–804.

Namur, M., J. M. Petit, D. Lagneaux, and R. Sneppe (1961). Variations de la saturation artérielle en $O_2$ au cours du cycle respiratoire. *Arch. Int. Physiol. Biochim.* 69: 731–736.

Nims, L. F. and C. Marshall (1938). Blood pH in vivo. I. Changes due to respiration. *Yale J. Biol. Med.* 10: 445–448.

Nye, R. E., Jr. (1970). Influence of the cyclical pattern of ventilatory flow on pulmonary gas exchange. *Respir. Physiol.* 10: 321–337.

Pain, M. C. F. and J. B. West (1966). Effect of the volume history of the isolated lung on distribution of blood flow. *J. Appl. Physiol.* 21: 1545–1550.

Pombo, J. F., B. L. Troy, and R. O. Russell, Jr. (1971). Left ventricular volume and ejection fraction by echocardiography. *Circulation* 63: 480–490.

Purves, M. J. (1966). Fluctuations of arterial oxygen tension which have the same period as respiration. *Respir. Physiol.* 1: 281–296.

Rossing, R. G. and S. M. Cain (1966). A nomogram relating $P_{O_2}$, pH, temperature, and hemoglobin saturation in the dog. *J. Appl. Physiol.* 21: 195–201.

Schuler, R. and F. Kreuzer (1967). Rapid polarographic in vivo oxygen catheter electrodes. *Respir. Physiol.* 3: 90–110.

Seed, W. A. and N. B. Wood (1971). Velocity patterns in the aorta. *Cardiovascular Res.* 5: 319–330.

Severinghaus, J. W. and M. Stupfel (1957). Alveolar dead space as as index of distribution of blood flow in pulmonary capillaries. *J. Appl. Physiol.* 10: 335–348.

Shaffer, A. B., M. Solorio, and H. Weinstein (1971). Pulmonary artery-left heart circulatory transfer function in hemorrhagic hypotension. *J. Appl. Physiol.* 31: 801–807.

Snedecor, G. W. and W. G. Cochran (1968). Statistical methods. Ames, Iowa, The Iowa State University Press, 6th ed. pp. 91–116 and 135–198.

Swan, H. J. C. and W. Beck (1960). Ventricular nonmixing as a source of error in the estimation of ventricular volume by the indicator-dilution technic. *Circulation Res.* 8: 989–998.

Thompson, H. K., Jr., C. F. Starmer, R. E. Whalen, and H. D. McIntosh (1964). Indicator transit time considered as a gamma variate. *Circulation Res.* 14: 502–515.

Wessel, H. U., G. W. James, and M. H. Paul (1966). Effects of respiration and circulation on central blood temperature of the dog. *Am. J. Physiol.* 211: 1403–1412.

West, J. B., C. T. Dollery, and A. Naimark (1964). Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *J. Appl. Physiol.* 19: 713–724.

Yamamoto, W. S. (1960). Mathematical analysis of time course of alveolar $CO_2$. *J. Appl. Physiol.* 15: 215–219.

Yamomoto, W. S. (1962). Transmission of information by the arterial blood stream with particular reference to carbon dioxide. *Biophysical J.* 2: 143–159.

Yokota, H. and F. Kreuzer (1970). Respiratory fluctuations of oxygen tension in central vessels of the dog. In: Fluid Dynamics of Blood Circulation and Respiratory Flow. AGARD Conference Proceedings No. 65. pp. 14/1–8.

Yokota, H., L. J. C. Hoofd, and F. Kreuzer (1973), Alveolar oxygen tension in anesthetized, artificially ventilated dogs. *Pflügers Arch., in press.*

Zierler, K. L. (1962). Circulation times and the theory of indicator-dilution methods for determining blood flow and volume. In: Handbook of Physiology. Section 2: Circulation. Vol. I, edited by W. F. Hamilton and P. Dow. Washington, D. C., American Physiological Society, pp. 585–615.

# *Chapter III*

## RESPIRATORY FLUCTUATIONS OF OXYGEN TENSION IN CENTRAL VENOUS BLOOD OF ANESTHETIZED DOGS*

**Abstract.** Venous $P_{O_2}$ was continuously recorded in the superior and inferior caval veins and in the pulmonary artery by a catheter $P_{O_2}$ electrode in the anesthetized dog breathing spontaneously or ventilated artificially. Venous $P_{O_2}$ showed fluctuations with the same period as respiration at all places of measurement The fluctuations were more pronounced in the inferior than in the superior caval vein, and largest just below the veno-atrial junction The amplitude of $P_{O_2}$ fluctuations in the pulmonary artery was smaller and did not show any correlation with breathing frequency, absolute value of $P\bar{v}_{O_2}$, and level of oxygenation. Blocking of the renal veins by tourniquets reduced the amplitude of the fluctuations below the veno-atrial junction, blocking of the caval flow below the liver flattened them, whereas blocking below the renal veins did not elicit any clear-cut effect These findings suggest a different effect of respiratory movement on the venous outflow from various organs (particularly the liver and the kidney), thus altering their relative contributions during the respiratory cycle

Dog
Oxygen tension
Respiration
Venous blood
Venous outflow

Variations of oxygenation in arterial blood were demonstrated by Bergman (1961) in open-chest dogs. Namur *et al.* (1961) also measured variations of arterial oxygen saturation in hypoxic man. More recently respiratory variations of arterial oxygen pressure were measured by Purves (1966) with a micro oxygen electrode incorporated into a flow-through cuvette in cats and new-born lambs and by the present authors (Yokota and Kreuzer, 1970) in dogs with a catheter oxygen electrode developed by Kimmich and Kreuzer (1969). All reports agree in attributing these respiratory variations of arterial oxygenation to those of alveolar air reported by Chilton *et al.* (1952, 1954), DuBois, Britt and Fenn (1952), and Yamamoto (1960).

The composition of mixed venous blood has always been assumed to be constant in steady state. However the existence of temperature variations in the pulmonary artery has been demonstrated by Afonso *et al.* (1962a,b) and Wessel, James and Paul (1966); these variations have been interpreted as being due to respiratory changes in

* *Respiration Physiology (1972) 15; 350-364.*

rate of venous outflow from various organs having different temperature. This interpretation suggests that the same phenomenon should occur in venous oxygen tension (Dejours *et al.*, 1966). This has been shown to be the case by Yokota and Kreuzer (1970). In the present paper we analyze data of these respiratory variations of venous oxygen tension in the dog under various circumstances in order to elucidate their possible components and causes.

## Methods

The experiments were performed in 24 mongrel dogs of either sex, weighing 16 to 32 kg, anesthetized by intravenous chloralose-urethane (for induction 25-50 mg/kg and 125–250 mg/kg, and for maintenance 5–10 mg/kg/hr and 25–50 mg/kg/hr, respectively) after premedication by intramuscular acepromazine (1 mg/kg). After intubation of the trachea the dog in supine position either breathed spontaneously or was ventilated with a volume-controlled pump (Harvard, model 607), receiving room air or gas mixtures containing 10, 60 or 100% $O_2$ in $N_2$.

Two blood-type catheter oxygen electrodes (Kimmich and Kreuzer, 1969) were introduced into the thoracic aorta and into the pulmonary artery from the femoral vessels, or into the caval veins from the right external jugular vein in order to record oxygen tension in arterial and venous blood continuously. The position of the oxygen electrode in the caval veins was changed in order to investigate the differences in oxygen tension along the caval veins, in the superior caval vein up to the aortic arch, in the inferior caval vein from just below the veno-atrial junction to above or below the renal veins. Hollow catheters were inserted through the femoral veins to the same location in the vessels as the oxygen electrodes for blood sampling and pressure measurement. In 6 dogs a catheter tip electromagnetic flowmeter (Skalar Instruments, Delft, 600 system) was introduced into the vicinity of the oxygen electrode in the inferior caval vein in order to compare variations of blood velocity and oxygen tension. All these catherizations were performed under fluoroscopic guidance. Coagulation of blood was prevented by intravenous heparin administration (2 ml of heparin solution containing 5000 units/ml) at the beginning and 3–4 hr later or when some sign of clotting was found in blood samples.

Respiration was recorded by a pneumotachograph. Gaseous $O_2$ and $CO_2$ were monitored by a gas-type catheter oxygen electrode (Schuler and Kreuzer, 1967; Beneken Kolmer and Kreuzer, 1968) placed in the tracheal tube and by an infrared $CO_2$ analyzer respectively. Arterial and venous blood pressure and intratracheal pressure were measured by Statham strain gauges. All these parameters were recorded on a Honeywell Visicorder 1108. Blood samples, taken during each *in vivo* $P_{O_2}$ recording after changing the inspiratory gas or the position of the $P_{O_2}$ electrode, were analyzed for $P_{O_2}$ and $P_{CO_2}$ with a blood gas analyzer (Radiometer, Copenhagen, type PHA 927) and for pH with a Radiometer pH meter 22 at $38 \pm 0.1$ °C. These electrodes were calibrated with tonometered blood and buffer solution respectively. When the body temperature of the dog, measured in the rectum by a mercury thermometer, was different from that of the blood gas analyzer, the measured blood gas

values were corrected according to Nunn *et al.* (1965).

Details of the blood-type oxygen electrode may be found elsewhere (Kimmich and Kreuzer, 1969). The actual calibration line was obtained by plotting the deflections against sample blood $P_{O_2}$ values obtained after changing the inspiratory oxygen concentration or the position of the catheter $P_{O_2}$ electrode. The amplitude of the respiratory $P_{O_2}$ fluctuations was read off from the calibration curve; when the fluctuations were changing in amplitude, the mean value between the largest and the smallest fluctuations was used to represent the fluctuation during the respective period.

Statistical treatment was performed with the t-test between 2 groups and with variance analysis among more than 2 groups. The limit of significance was assumed at $p=0.05$. The following abbreviations are used in this paper: oxygen tension = $P_{O_2}$; arterial oxygen tension = $Pa_{O_2}$; venous oxygen tension = $Pv_{O_2}$; mixed venous oxygen tension = $P\bar{v}_{O_2}$; superior caval vein = VCS; inferior caval vein = VCI.

## Results

Almost all records of $P_{O_2}$ in the caval veins and in the pulmonary artery showed fluctuations having the same period as respiration during spontaneous breathing and during artificial ventilation. Apart from these respiratory fluctuations, $Pv_{O_2}$ sometimes showed cyclic variations accompanying vasomotor waves in arterial pressure as shown in fig. 1. Moreover even without any variation in other parameters the $P_{O_2}$ in the VCI occasionally showed a slow and irregular undulation, ranging over several breaths to several minutes, superimposed on the respiratory fluctuations; the amplitude of the latter showed, in such a case, a periodic variation in connection with the phase of the undulation. In this paper we have focused our attention to those fluctuations of $P_{O_2}$ which have the same period as respiration.

### EVENTS IN THE CAVAL VEINS; SPONTANEOUS BREATHING

Figure 2 shows a record of respiratory fluctuations of $P_{O_2}$ in the thoracic VCI (left) and in the VCS (right). Their pattern and amplitude were variable with time; in 2 out of 16 dogs the respiratory fluctuations observed in the earlier period of the experiment disappeared thereafter; the data from one of these 2 dogs were not included because of technical difficulties. There were also variations in pattern and amplitude of the $P_{O_2}$ fluctuations along the caval veins accompanied by changes of mean $Pv_{O_2}$. In table 1 the mean values of $P_{O_2}$ in 4 places of the caval veins and the amplitudes of its fluctuations are listed. The highest $P_{O_2}$ was found in the VCI above the renal veins and the second highest in the VCS but these two values did not show a significant difference. $P_{O_2}$ in the thoracic VCI and below the renal veins was significantly lower than in the two locations mentioned. On the other hand the largest fluctuation of $P_{O_2}$ was found in the thoracic VCI; it differed significantly from that in the adjoining abdominal VCI and the VCS where the fluctuation was the smallest.

The fluctuations in the abdominal caval vein, either above or below the renal veins, showed rather unstable and variable patterns. In one dog the $P_{O_2}$ record above the renal veins showed an utterly irregular excursion with no relation to respiration. In

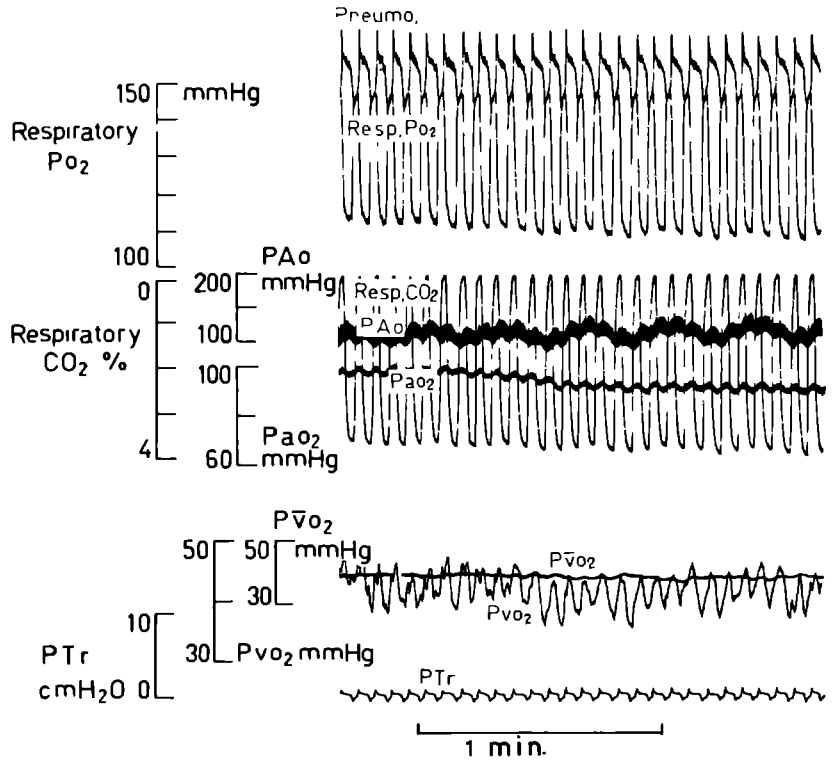



Fig. 1. Periodic changes of the amplitude of $P_{O_2}$ fluctuations in the abdominal caval vein above the renal veins accompanying vasomotor waves in arterial pressure Tracings from top to bottom: pneumotachogram (Pneumo), respiratory $P_{O_2}$ (Resp. $P_{O_2}$), respiratory $CO_2$ (Resp. $CO_2$), aortic blood pressure ($P_{A_O}$), arterial $P_{O_2}$ ($Pa_{O_2}$), mixed venous $P_{O_2}$ ($P\bar{v}_{O_2}$), $P_{O_2}$ in the abdominal caval vein above the renal veins ($Pv_{O_2}$), and intratracheal pressure (Ptr). The dog was breathing room air spontaneously.

the thoracic VCI the fluctuations of $P_{O_2}$ were relatively stable and showed a common phasic relationship to respiration, although there were some varieties in detail, namely a trough or a dip in late inspiration to early expiration and a plateau or a peak during the expiratory pause. Also in most dogs a rapid fall of $P_{O_2}$ was recorded during inspiration, as shown in fig. 2, where the blood velocity was increased. With the elongation of the expiratory pause the shoulders of the plateau were rounded off and/or small and irregular ripples were superimposed on the plateaux; with the increase of the breathing frequency the upward excursion of the fluctuation became more like a peak, while the trough was barely affected. There was no correlation between the amplitudes of the $P_{O_2}$ fluctuations in the thoracic VCI and the breathing frequency during spontaneous ventilation ($p > 0.05$).

## EFFECT OF DIFFERENT INSPIRATORY OXYGEN CONCENTRATION

Results with either 10% or 100% $O_2$ are listed in table 2. Comparison of tables 1 and

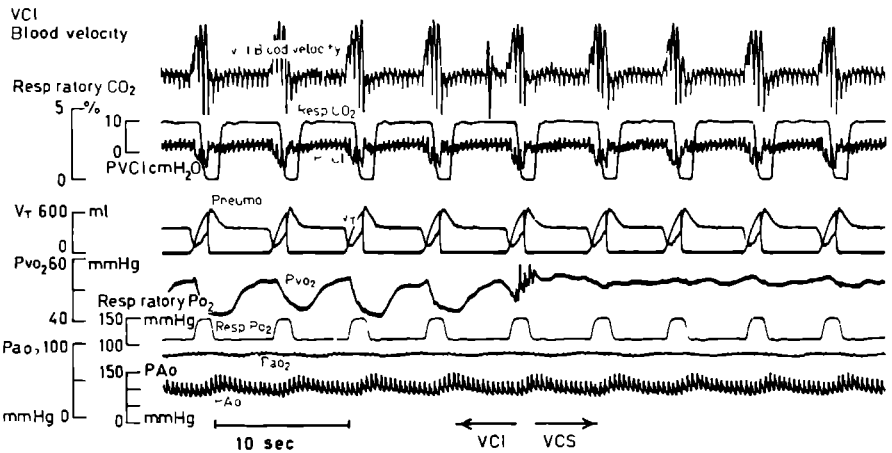



Fig 2 Respiratory fluctuations of $P_{O_2}$ in the thoracic caval vein of a dog breathing room air spontaneously The $P_{O_2}$ electrode was moved from the inferior caval vein on the left half to the superior caval vein on the right Tracings from top to bottom inferior caval venous blood velocity (VCI blood velocity), respiratory $CO_2$ (Resp $CO_2$), blood pressure in the thoracic inferior caval vein (PVCI), pneumotachogram (Pneumo ), tidal volume ($V_T$) $P_{O_2}$ in the thoracic caval vein ($Pv_{O_2}$) respiratory $P_{O_2}$ (Resp $P_{O_2}$) arterial $P_{O_2}$ ($Pa_O$ ) and aortic blood pressure ($P_{A_O}$)

TABLE 1

Oxygen tension ($P_{O_2}$) amplitude of its respiratory fluctuations ($\Delta P_{O_2}$), and ratio of $\Delta P_O$ /$P_{O_2}$ in percent in the caval veins of dogs breathing room air spontaneously VCS superior caval vein VCI inferior caval vein, S D standard deviation n number of experiments p values obtained by applying paired t test $P_{O_2}$ values in mm Hg

| | VCS | | | thoracic VCI | | | VCI above renal veins | | | VCI below renal veins | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $P_{O_2}$ | $\Delta P_{O_2}$ | % | $P_{O_2}$ | $\Delta P_{O_2}$ | % | $P_{O_2}$ | $\Delta P_{O_2}$ | % | $P_{O_2}$ | $\Delta P_{O_2}$ | % |
| mean | 50 4 | 1 1 | 2 1 | 45 2 | 6 9 | 15 1 | 52 1 | 3 9 | 7 6 | 45 1 | 1 4 | 3 3 |
| S D | 7 8 | 0 4 | 1 3 | 6 8 | 3 1 | 7 9 | 7 7 | 3 4 | 6 3 | 9 5 | 0 8 | 3 6 |
| n | 24 | 24 | 24 | 28 | 28 | 28 | 18 | 17 | 17 | 17 | 17 | 17 |
| p | | | | | | | | | | | | |
| $P_{O_2}$ | | | < 0 001 | | | < 0 001 | | | < 0 001 | | | |
| $\Delta P_{O_2}$ | | | < 0 001 | | | < 0 01 | | | < 0 05 | | | |
| % | | | < 0 001 | | | < 0 01 | | | < 0 05 | | | |

2 shows that the increase of inspiratory $O_2$ concentration from hypoxia to hyperoxia induced an increase of $P_{O_2}$ in all positions examined ($p < 0\,01$ for all positions in the caval veins), the amplitude of the respiratory fluctuation increased too in the VCS and the thoracic VCI ($p < 0\,01$ for both locations), but not in the abdominal caval vein The pattern of fluctuation was almost uninfluenced by the administration of

TABLE 2

Oxygen tension ($P_{O_2}$) and amplitude of its respiratory fluctuations ($\Delta P_{O_2}$) in the caval veins of dogs breathing either 10% or 100% of $O_2$ spontaneously VCS superior caval vein, VCI inferior caval vein, S D standard deviation, n number of experiments p values obtained by applying paired t-test n s not significant $P_{O_2}$ values in mm Hg

| | VCS | | thoracic VCI | | VCI above renal veins | | VCI below renal veins | |
|---|---|---|---|---|---|---|---|---|
| | $P_{O_2}$ | $\Delta P_{O_2}$ | $P_{O_2}$ | $\Delta P_{O_2}$ | $P_{O_2}$ | $\Delta P_{O_2}$ | $P_{O_2}$ | $\Delta P_{O_2}$ |
| 10% $O_2$ | | | | | | | | |
| mean | 37 5 | 0 6 | 33 7 | 4 1 | 40 7 | 2 5 | 36 1 | 1 3 |
| S D | 5 8 | 0 5 | 5 4 | 3 4 | 5 7 | 3.9 | 7 9 | 1 5 |
| n | 8 | 8 | 8 | 8 | 5 | 5 | 5 | 5 |
| p | | | | | | | | |
| $P_{O_2}$ | | < 0 05 | | < 0 01 | | < 0 05 | | |
| $\Delta P_{O_2}$ | | < 0 02 | | n s | | n s | | |
| 100% $O_2$ | | | | | | | | |
| mean | 57 2 | 2 1 | 53 3 | 12 5 | 70 3 | 2 9 | 58 5 | 2 1 |
| S D | 9 3 | 1 9 | 9 7 | 6 1 | 14 2 | 2 3 | 11 9 | 2 7 |
| n | 8 | 8 | 8 | 8 | 5 | 4 | 5 | 4 |
| p | | | | | | | | |
| $P_{O_2}$ | | n s | | < 0 02 | | < 0 05 | | |
| $\Delta P_{O_2}$ | | < 0 01 | | < 0 02 | | n s | | |

hypoxic or hyperoxic gas; in hypoxia the plateaux were somewhat sharper or narrower with increased breathing frequency; in hyperoxia the plateaux were sometimes superimposed by small waves with elongation of the expiratory pause. Whatever the inspiratory $O_2$ concentration there was a constant tendency in $P_{O_2}$ variation along the VCI in the sense that the highest $P_{O_2}$ was found above the renal veins and the largest fluctuation in the thoracic part.

### EFFECT OF POSITIVE PRESSURE VENTILATION

Four dogs were ventilated with a Harvard pump after collection of data during spontaneous breathing; muscular relaxation was attained by intravenous administration of Alloferin (Roche), 100 μg/kg. Ventilatory volume was adjusted to keep the same $P_{O_2}$ as during spontaneous breathing. There was no marked difference between the findings during spontaneous and artificial ventilation; the largest fluctuation was recorded in the thoracic VCI (mean fluctuation 7.1 mm Hg, ranging from 4.3 to 11.4 mm Hg); in the VCS and the VCI below the renal veins only small fluctuations

were found up to 1.2 and 3.4 mm Hg, respectively. In the VCI above the renal veins the fluctuations were intermediate to those mentioned above (mean 4.5 mm Hg, ranging from 2.4 to 7.7 mm Hg). The only difference was seen in the thoracic VCI; the common phasic relationship between fluctuation and respiratory cycle, which was present during spontaneous breathing, was no longer observed here; each dog showed fluctuations with different phasic relationship to respiration.

### EFFECT OF BREATH HOLDING

Air flow was stopped in 3 dogs for 10 to 20 sec by obstructing the tracheal tube during spontaneous breathing or stopping the respiration pump at inspiratory or expiratory level. On cessation of ventilatory movement the cyclic fluctuations of $P_{O_2}$ almost disappeared and in some cases a slow undulation or small ripples were observed. During spontaneous breathing the ventilatory movement could not be stopped by this maneuver at the expiratory level, but a vigorous inspiratory effort occurred and therefore the $P_{O_2}$ fluctuations continued. In the thoracic VCI the $P_{O_2}$ stopped fluctuating at the level of the plateau in 2 dogs and ascended gradually from a trough in the other dog after inspiratory breath holding. On the other hand the $P_{O_2}$ in the VCI above the renal veins was maintained at a lower level near the trough in all 3 dogs during inspiratory breath holding (fig. 3).

During artificial ventilation the pattern obtained after inspiratory breath holding was different; the $P_{O_2}$ fluctuations disappeared at the level of the trough in the thoracic VCI and at the level of the plateau in the VCI above the renal veins (fig. 3). With expiratory breath holding during artificial ventilation there was no consistent pattern of $P_{O_2}$ change; in one case there was a rise from a trough, in another one a descent from a plateau, or an adjustment at a certain level. In all cases the restoration of ventilation was followed by the revival of cyclic fluctuations observed before the breath holding.

### EFFECT OF BLOCKING VENOUS RETURN ON RESPIRATORY FLUCTUATIONS OF $P_{O_2}$ IN THE THORACIC VCI

In order to elucidate the effect of venous return from various organs on the respiratory fluctuations of $P_{O_2}$ in the thoracic VCI, the renal veins, the VCI below the renal veins, or both were blocked temporarily by tourniquets placed through a midline incision of the abdomen in 2 dogs breathing room air or gas mixtures with different $O_2$ concentration spontaneously. The abdominal incision was closed again around the tubes with the tourniquets ready for blocking. This operation did not change the pattern of respiratory fluctuations of $P_{O_2}$ in the thoracic VCI. The results are listed in table 3. Blocking of the renal veins with or without blocking of the VCI below the renal veins induced a diminution of $P_{O_2}$ and of its fluctuations in the thoracic VCI, whereas blocking of the VCI below the renal veins showed no significant influence in general. Figure 4 shows a record where the respiratory fluctuations of $P_{O_2}$ almost disappeared after the blocking of the renal veins and the VCI below them. As may be seen from the record the fluctuation pattern was changed mainly by lowering of the plateau, whereas

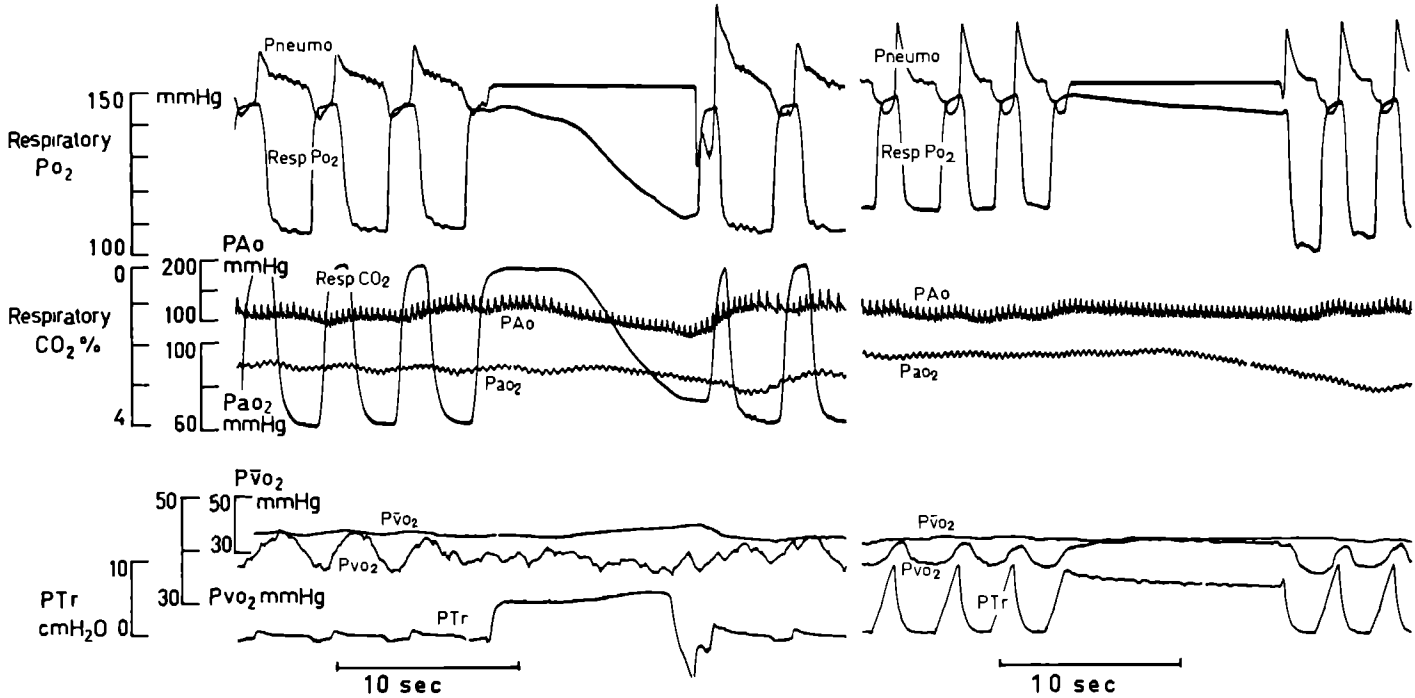



Fig. 3 Effect of inspiratory breath holding on respiratory fluctuations of $P_{O_2}$ in the abdominal caval vein of a dog breathing spontaneously on the left and being ventilated artificially on the right. Tracings from top to bottom: pneumotachogram (Pneumo.), respiratory $P_{O_2}$ (Resp. $P_{O_2}$), respiratory $CO_2$ (Resp. $CO_2$), aortic blood pressure (PAo), arterial $P_{O_2}$ ($Pa_{O_2}$), mixed venous $P_{O_2}$ ($P\bar{v}_{O_2}$), $P_{O_2}$ in the abdominal caval vein above the renal veins ($Pv_{O_2}$), and intratracheal pressure (PTr).

TABLE 3

Effect of blocking of venous return from the renal veins and the inferior caval vein (VCI) below the renal veins on the respiratory fluctuations of $P_{O_2}$ in the thoracic VCI in 2 dogs breathing spontaneously at various oxygenation levels $P_{O_2}$ values in mm Hg p values obtained by applying paired t-test

| inhaled $O_2$ | control | | after blocking of | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | renal veins | | VCI below renal veins | | + VCI below renal veins | |
| | $P_{O_2}$ | $\Delta P_{O_2}$ | $P_{O_2}$ | $\Delta P_{O_2}$ | $P_{O_2}$ | $\Delta P_O$ | $P_{O_2}$ | $\Delta P_{O_2}$ |
| 10% | 32 5 | 1 6 | 29 5 | 0 | 29 5 | 1 3 | | |
| | 38 0 | 3 6 | 37 1 | 1 5 | 39 0 | 2 3 | 34 2 | 3 0 |
| 21% | 50 3 | 5 2 | 45 3 | 0 | 52 3 | | | |
| | 54 0 | 10 4 | 46 9 | 5 2 | 51 9 | 9 8 | 43 7 | 1 6 |
| | 53 2 | 6 0 | 50 4 | 3 5 | 58 0 | 3 0 | 49 0 | 1 5 |
| | 48 0 | 3 8 | 44 0 | 3 1 | 46 6 | irregular | 43 0 | 1 5 |
| 60% | 55 4 | 9 1 | 52 3 | 1 3 | 50 1 | 14 3 | | |
| | 69 5 | 8 3 | 61 3 | 1 5 | 75 6 | 4 5 | 57 1 | 2 7 |
| 100% | 86 3 | 13 0 | 58 8 | 1 0 | | | | |
| | 69 5 | 7 5 | | | 69 5 | 12 0 | 60 8 | 1 9 |
| p | | | < 0 05 | < 0 01 | n s | n s | < 0 01 | < 0 02 |

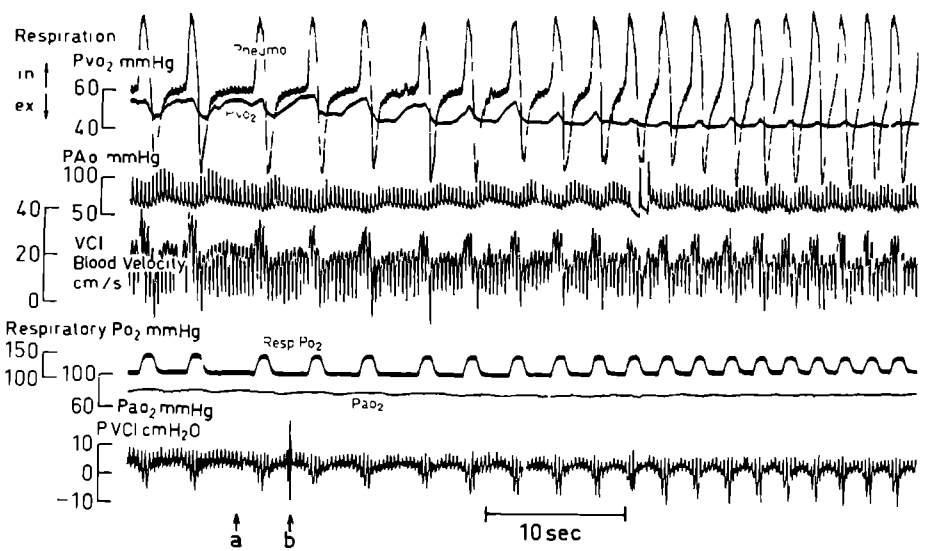



Fig 4 Effect of blocking abdominal venous return on respiratory fluctuations of $P_{O_2}$ in the thoracic inferior caval vein Arrows a and b indicate the time of closure of the renal veins and of the caval veins below the renal veins, respectively Tracings from top to bottom pneumotachogram (Pneumo ), $P_{O_2}$ in the thoracic inferior caval vein ($Pv_{O_2}$), aortic blood pressure (PAO), blood velocity in the thoracic inferior caval vein, respiratory $P_{O_2}$ (Resp $P_{O_2}$), arterial $P_{O_2}$ ($Pa_{O_2}$), and blood pressure in the thoracic inferior caval vein (PVCI)

the trough was almost unaffected or lowered only slightly. During the blocking of venous return for 40 to 60 sec breathing frequency was increased and blood velocity in the thoracic VCI decreased slightly, yet showing clear inspiratory increment. Also arterial blood pressure was lowered somewhat but not below 75 mm Hg (mean pressure) in 9 blocking runs out of 10 whereas it reached 60 mm Hg in one run. After release of the tourniquets the previous fluctuations were restored within 30 to 60 sec following a temporary fall of $Pv_{O_2}$.

## EVENTS IN THE PULMONARY ARTERY

In most cases fluctuations of $P_{O_2}$ were also observed in the pulmonary artery, though smaller than in the VCI. Figure 5 shows a record of $P\bar{v}_{O_2}$ with other parameters of a dog breathing room air spontaneously. The pattern and the amplitude were also rather variable here. However, the most predominant pattern observed during spontaneous respiration was a rise of $P_{O_2}$ during inspiration and a fall during expiration. Sometimes the descending portion of the fluctuation showed a sharp fall which might be comparable to that in the thoracic VCI. There was no clear difference in the pattern and the amplitude of fluctuations between spontaneous and artificial ventilation, except that the position of the plateau in artificially ventilated dogs was more widely scattered in one respiratory cycle than during spontaneous ventilation. The mean values of $P\bar{v}_{O_2}$ and the amplitude of its fluctuations at various oxygenation levels

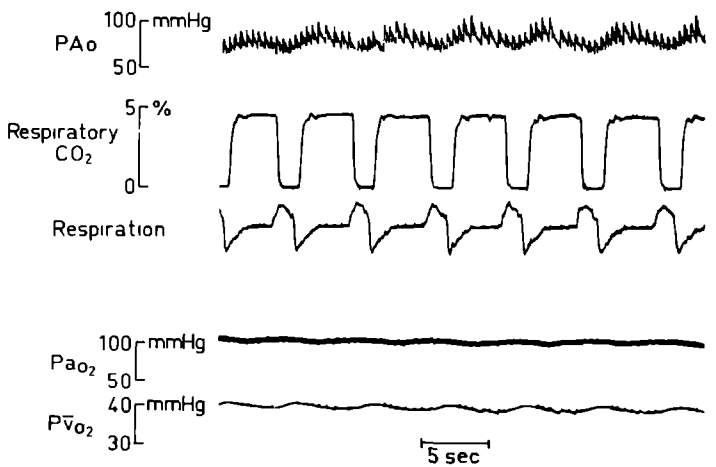



Fig 5 Respiratory fluctuations of mixed venous $P_{O_2}$ ($P\bar{v}_{O_2}$) Tracings from top to bottom: aortic blood pressure (PAo), respiratory $CO_2$, pneumotachogram, arterial $P_{O_2}$ ($Pa_{O_2}$), and mixed venous $P_{O_2}$ ($P\bar{v}_{O_2}$)

are presented in table 4. With increase of inspiratory $O_2$ concentration the $P\bar{v}_{O_2}$ during either spontaneous or artificial ventilation increased significantly ($p < 0.01$) and the fluctuations showed the same tendency though the differences were not significant.

TABLE 4

Oxygen tension ($P_{O_2}$) and amplitude of its respiratory fluctuations ($\Delta P_{O_2}$) in the pulmonary artery of dogs during spontaneous or artificial ventilation at various oxygenation levels $P_{O_2}$ values in mm Hg. S.D.: standard deviation, n: number of experiment.

| inhaled $O_2$ | 10% | | 21% | | 60% | | 100% | |
|---|---|---|---|---|---|---|---|---|
| | $P_{O_2}$ | $\Delta P_{O_2}$ | $P_{O_2}$ | $\Delta P_{O_2}$ | $P_{O_2}$ | $\Delta P_{O_2}$ | $P_{O_2}$ | $\Delta P_{O_2}$ |
| spontaneous respiration | | | | | | | | |
| mean | 30.1 | 0.9 | 43 4 | 1 0 | 50.6 | 4.5 | 54.1 | 1.3 |
| S.D. | 5.0 | 0.8 | 4.6 | 0.9 | 5.0 | 6 2 | 3.7 | 1 3 |
| n | 4 | 4 | 13 | 13 | 8 | 8 | 8 | 8 |
| artificial ventilation | | | | | | | | |
| mean | 22 4 | 0 2 | 35 7 | 1 8 | 38.3 | 1.4 | 46 1 | 2.5 |
| S.D. | 3.7 | 0 3 | 3 9 | 2.2 | 6 1 | 1 0 | 6.9 | 3.0 |
| n | 3 | 3 | 9 | 9 | 7 | 7 | 7 | 7 |

## Discussion

Even though the catheter oxygen electrode used in our experiments has a much reduced flow sensitivity, it is still not quite negligible when the flow velocity changes in the range below 10 cm/sec. In order to examine a possible influence of flow changes on the electrode, the blood velocity in the VCI was measured simultaneously with a catheter tip electromagnetic flowmeter in the vicinity of the oxygen electrode (within 1–2 cm). As shown in figs. 2 and 5, a rapid fall of $P_{O_2}$ occurred during early inspiration where the blood velocity showed a clear increase and there was no systematic relationship between the directions of the changes in blood velocity and the excursions of $Pv_{O_2}$ during the respiratory cycle. Also the distinct difference in the fluctuations of $Pv_{O_2}$ between the VCS and the thoracic VCI, where the blood flow changes in the same manner with respiration (Mixter, 1953; Brecher and Mixter, 1953), indicates that the flow artefact is negligible in the velocity range of caval blood flow. This electrode is not sensitive to pressure.

Variations of temperature in the central veins with respiration reported by Afonso *et al.* (1962a, b) and Wessel *et al.* (1966) might have to be considered as another possible cause of artefact. Yet these variations of venous temperature are not more than 0.2 °C in the thoracic VCI and would create a change of the electrode output by only 2% of the total deflection whereas the mean fluctuation of $P_{O_2}$ amounts to 15.6%; they can therefore be neglected. Moreover the reality of these respiratory $P_{O_2}$ fluctuations was confirmed in 5 dogs by paired blood samples collected manually in very small steps from the thoracic VCI, one corresponding to the plateau and the other to the trough of the $P_{O_2}$ record. In 15 out of 17 pairs of samples the same directional change of $P_{O_2}$ was found as that of the recorded fluctuations which were ranging from 3.6 mm

Hg to 19.6 mm Hg; in 12 out of these 15 paired samples the difference of $P_{O_2}$ was larger than 40% of the amplitude of the recorded fluctuations. From 2 pairs we could not find any difference of $P_{O_2}$, whereas the records of these 2 sampling periods showed unstable fluctuations superimposed by slow undulation of $P_{O_2}$. When there was a clear difference of $P_{O_2}$ in a pair of samples, also a difference in $P_{CO_2}$ of nearly the same order and in pH of the order of one hundredth unit was found.

Furthermore the $P_{O_2}$ electrode might be displaced by the respiratory movements to different parts of the vascular cross sectional area which might carry lamellae of blood stream with different $P_{O_2}$ in the presence of laminar flow. However, this effect is unlikely to explain the fluctuations of $P\bar{v}_{O_2}$ seen in the pulmonary artery because the blood from both caval veins is sufficiently mixed when it reaches the main pulmonary arteries (Vliers and Zijlstra, 1969), even though the mixing in the right ventricle may be incomplete (Maseri and Enson, 1968). During the experiments it was observed fluoroscopically that the electrode in the thoracic VCI was displaced with every heart beat. This finding suggests that the electrode was not located in any one particular lamella of blood stream even during one heart beat, let alone during a specific period of the respiratory cycle. Furthermore this beat-to-beat displacement of the electrode will disturb laminar flow and tend to promote mixing.

It is difficult to say what influence anesthesia may have on the patterns described here. Although chloralose-urethane anesthesia is generally agreed to have only weak effects on the circulatory system, it influences the autonomic nervous system and inhibits the secretion of adrenaline (Balis and Monroe, 1964). A subsequent redistribution of blood flow through various organs cannot be excluded. However, almost the same patterns of thermal gradients in the vascular system and of respiratory temperature variations are reported in dogs with various kinds of anesthesia (Horvath, Rubin and Foltz, 1950; Afonso *et al.*, 1962b; Wessel *et al.*, 1966) and in man (Afonso *et al.*, 1962a). Therefore an important alteration by anesthesia seems unlikely in our experiments.

In preliminary experiments on 3 dogs we found the highest $P_{O_2}$ in the renal veins and the lowest in the hepatic veins. This may explain the course of $P_{O_2}$ and its respiratory fluctuations along the VCI on the basis of the relative contributions from various organs during a respiratory cycle (similar to the respective temperature changes).

There has been general agreement since Mixter (1953) and Brecher and Mixter (1953) that inspiration accelerates venous return in the thoracic caval veins. However the influence of respiration on venous drainage from the liver has been controversial. Ever since Hales (quoted by Alexander, 1951) the descent of the diaphragm had been considered to squeeze blood from the abdominal viscera into the thoracic caval vein (Eckstein, Wiggers and Graham, 1947; Alexander, 1951; Selkurt and Brecher, 1956; Norhagen, 1963). Other reports have contradicted this hypothesis, *i.e.*, inspiratory decrease or arrest of hepatic venous flow was reported (Brauer, McElroy and Leong, 1960; Moreno, 1964; Grabner, 1963; Neumayr, 1964; Moreno *et al.*, 1967). Bradley (1963) suggested a compromise between these contradictory views in that extraneous factors like respiratory rate, body position, body size, etc., might alter

the response of hepatic venous flow to respiration.

The respiratory fluctuations of $P_{O_2}$ in the thoracic VCI are characterized by: 1) during spontaneous ventilation there was a rapid fall of $P_{O_2}$ in early inspiration in almost all cases; 2) by blocking renal outflow the mean $P_{O_2}$ and the amplitude of fluctuations decreased; 3) blocking renal and lower caval venous flow abolished the fluctuations and $P_{O_2}$ was maintained at the level of the trough or somewhat lowered, the thoracic VCI being supplied mostly by blood from the liver. These observations suggest that the rate of contribution from the liver to the VCI increases during inspiration, at least in its early period, when the dog breathes spontaneously. However, the respiratory influence on hepatic outflow is not equal in all circumstances since we observed in 2 dogs that the respiratory fluctuations of $P_{O_2}$ in the thoracic VCI disappeared during the experiment.

Venous return from retroperitoneal organs, e.g., the kidneys or the pelvic organs, and from the legs is also supposed to be under the influence of respiratory variations of abdominal pressure and to create the fluctuations of $P_{O_2}$ as demonstrated above. In the abdominal caval vein, however, we could not find any consistent phasic relationship between the pattern of $P_{O_2}$ fluctuations and respiration as was the case in the thoracic VCI. This may be partly explained by the fact that the difference in respiratory pattern causes a variety of intraabdominal pressure changes (Campbell and Green, 1953), *e.g.*, synchronous decrease with inspiration (Moreno *et al.*, 1967) or increase during inspiration (Mixter, 1953; Norhagen, 1963; Morgan *et al.*, 1966).

In view of the far larger fluctuations of $P_{O_2}$ in the thoracic VCI than in the VCS, the fluctuations of $P_{O_2}$ in the pulmonary artery should be attributed mainly to venous return from the VCI. The respiratory fluctuations of inferior caval venous $P_{O_2}$ are first attenuated by blood from the VCS, the $P_{O_2}$ fluctuations of which are not only smaller but also sometimes different in phase from those in the VCI, then by the residual volume of the right heart, even though the effect may be small (Maseri and Enson, 1968), and finally by mixing in the initial part of the pulmonary artery. These composite mixing processes result in greatly attenuated $P_{O_2}$ fluctuations in the pulmonary artery as reported here.

## References

Afonso, S., G. G. Rowe, C. A. Castillo and C. W. Crumpton (1962a) Intravascular and intracardiac blood temperatures in man. *J. Appl. Physiol.* 17: 706–708

Afonso, S., J. F. Herrick, W. B. Youmans, G. G. Rowe and C. W. Crumpton (1962b) Temperature variations in the venous system of dogs. *Am. J. Physiol.* 203: 278–282

Alexander, R. S. (1951) Influence of the diaphragm upon portal blood flow and venous return. *Am. J. Physiol.* 167: 738–748

Balis, G. U. and R. R. Monroe (1964) The pharmacology of chloralose, a review. *Psychopharmacologia* 6: 1–30

Beneken Kolmer, H. H. and F. Kreuzer (1968) Continuous polarographic recording of oxygen pressure in respiratory air. *Respir. Physiol.* 4: 109–117

Bergman, N. A. (1961) Cyclic variations in blood oxygenation with the respiratory cycle. *Anesthesiol.* 22: 900–908

Bradley S F (1963) The hepatic circulation In Handbook of Physiology Section 2 Circulation Vol II, edited by W F Hamilton and P Dow Washington, D C American Physiological Society pp 1387 1438

Brauer, R W R F McElroy Jr and G F Leong (1960) Blood flow in the hepatic veins of the rat *Physiologist* 3 28

Brecher, G A and G Mixter Jr (1953) Effect of respiratory movements on superior cava flow under normal and abnormal conditions *Am J Physiol* 172 457-461

Campbell E J M and J H Green (1953) The variations in intra-abdominal pressure and the activity of the abdominal muscles during breathing, a study in man *J Physiol (London)* 122 282-290

Chilton A B and R W Stacy (1952) A mathematical analysis of carbon dioxide respiration in man *Bull Math Biophys* 14 1 18

Chilton A B, D S Barth and R W Stacy (1954) A mathematical analysis of oxygen respiration in man *Bull Math Biophys* 16 1 14

Dejours P, R Puccinelli, J Armand and M Dicharry (1966) Breath-to-breath variations of pulmonary gas exchange in resting man *Respir Physiol* 1 265–280

DuBois, A B, A G Britt and W O Fenn (1952) Alveolar $CO_2$ during the respiratory cycle *J Appl Physiol* 4 535 548

Eckstein, R W, C J Wiggers and G R Graham (1947) Phasic changes in inferior cava flow of intravascular origin *Am J Physiol* 148 740 744

Grabner, G (1963) Einige methodische, pathophysiologische und klinische Probleme des enterohepatalen Kreislaufes *Wien Z Inn Med* 44 221 305

Horvath S M A Rubin and E L Foltz (1950) Thermal gradients in the vascular system *Am J Physiol* 161 316–322

Kimmich, H P and F Kreuzer (1969) Catheter $P_{O_2}$ electrode with low flow dependency and fast response In Oxygen Pressure Recording in Gases, Fluids and Tissues, edited by F Kreuzer Progr in Resp Res Vol 3, edited by H Herzog Basel, Karger, pp 100–110

Maseri, A and Y Enson (1968) Mixing in the right ventricle and pulmonary artery in man Evaluation of ventricular volume measurements from indicator washout curves *J Clin Invest* 47 848–859

Mixter, G, Jr (1953) Respiratory augmentation of inferior vena caval flow demonstrated by a low-resistance phasic flowmeter *Am J Physiol* 172 446–456

Moreno A H (1964) Perpetuation of cirrhotic ascites as a result of altered regulation of venous return *Bull N Y Acad Med* 40 80

Moreno A H, A R Burchell R van der Woude and J H Burke (1967) Respiratory regulation of splanchnic and systemic venous return *Am J Physiol* 213 455–465

Morgan B C, F L Abel, G L Mullins and W G Guntheroth (1966) Flow patterns in cavae, pulmonary artery, pulmonary vein and aorta in intact dogs *Am J Physiol* 210 903-909

Namur, M J M Petit, D Lagneaux and R Sneppe (1961) Variations de la saturation arterielle en $O_2$ au cours du cycle respiratoire *Arch Int Physiol Biochim* 69 731 736

Neumayr A A (1964) Problems of the hepatic circulation in health and disease *Gastroenterology* 47 343 353

Norhagen A (1963) Selective angiography of the hepatic veins *Acta Radiol* Suppl 221 1–121

Nunn J F, N A Bergman, A Bunatyan and A J Coleman (1965) Temperature coefficients for $P_{CO_2}$ and $P_{O_2}$ of blood *in vitro J Appl Physiol* 20 23–26

Purves, M J (1966) Fluctuations of arterial oxygen tension which have the same period as respiration *Respir Physiol* 1 281–296

Schuler R and F Kreuzer (1967) Rapid polarographic *in vivo* oxygen catheter electrodes *Respir Physiol* 3 90 110

Selkurt, E E and G A Brecher (1956) Splanchnic hemodynamics and oxygen utilization during hemorrhagic shock in the dog *Circulation Res* 4 693–704

Vliers A C A P and W G Zijlstra (1969) Zum Problem der Mischung von Indikator und Blut *Z Kreislauffforsch* 58 79 88

Wessel, H U, G W James and M H Paul (1966) Effects of respiration and circulation on central blood temperature of the dog *Am J Physiol* 211 1403–1412

Yamamoto, W S (1960) Mathematical analysis of the time course of alveolar $CO_2$ *J Appl Physiol* 15 215–219

Yokota, H and F Kreuzer (1970) Respiratory fluctuations of oxygen tension in central vessels of the dog In Fluid Dynamics of Blood Circulation and Respiratory Flow AGARD Conference Proc 65 North Atlantic Treaty Organization, Advisory Group for Aerospace Research and Development, pp 14/1–14/8

# *Chapter IV*

## INFLUENCE OF BODY POSITION AND PNEUMOPERITONEUM ON RESPIRATORY VARIATION OF VENOUS RETURN IN ANESTHETIZED DOGS*

**Abstract.** Blood flow in the vena cava was measured in anesthetized dogs in supine, lateral, or prone position by a catheter velocity probe at four levels, i.e., above and below the veno-atrial junction and above and below the confluence of the renal veins, with the diameter of the vena cava fixed by Teflon rings placed around it. Also the influence of pneumoperitoneum at atmospheric pressure on venous return was examined in supine position. In supine position there was an increase of venous return in the thoracic venae cavae and of calculated hepatic outflow during inspiration, whereas flow in the abdominal vena cava showed less and reversed variations as compared with the thoracic inferior caval venous pattern, i. e , a trough during inspiration and a peak during early expiration. Pneumoperitoneum reduced the inspiratory increase of thoracic inferior vena cava flow and of hepatic outflow. Lateral and prone positions induced a decrease or early leveling off of the inspiratory increase of flow in the thoracic inferior vena cava and of hepatic outflow. Superior caval venous flow remained almost unchanged with postural change. In all positions renal outflow did not show any clear-cut relationship with respiration. These variations of pattern of vena cava flow and hepatic outflow were attributed to an increase in the resistance of the vena cava in the infradiaphragmatic part, induced by the change of body position, as shown by an increase of the preinspiratory caval venous pressure difference between thorax and abdomen to 5.3 $\pm$ 0 92 cm $H_2O$ (mean $\pm$ S D , n = 14) in lateral position, and to 6.5 $\pm$ 0 81 cm $H_2O$ (n = 4) in prone position from 2 0 $\pm$ 0 85 cm $H_2O$ (n = 18) in supine position ($p<0.001$ for the increase from supine position).

Venous return
Respiratory variation
Body position
Pneumoperitoneum
Dog

Inspiratory descent of the diaphragm and increase of abdominal pressure have been supposed already by Hales (1733, quoted by Franklin, 1937), and later by Eckstein *et al.* (1947), Alexander (1951), and Selkurt and Brecher (1956) to increase the venous return through the inferior vena cava (IVC), due to squeezing of blood from the visceral organs. Increase of venous return during inspiration was shown by Mixter (1953) as well as Brecher and Mixter (1953). Since the work of Brecher (1956) the relationship between respiration and the caval venous flow pattern seems to be firmly established. The behavior of hepatic outflow with respiration, however, has been a point of dispute despite its large contribution to IVC. Brauer *et al.* (1960) and Moreno (1964) demonstrated inspiratory arrest and expiratory increase of hepatic venous flow by cineangiography, Neumayr (1964) and Grabner (1963) measured expiratory

* *Pflugers Archiv (1973), in press.*

increase of hepatic venous flow by a thermocatheter, and more recently Moreno *et al.* (1967) calculated hepatic outflow as being decreased during inspiration, whereas Franklin (1937) found inspiratory increase and Norhagen (1963) expiratory reflux of hepatic blood. The present authors (Yokota and Kreuzer, 1972) observed cyclic variations of oxygen pressure in the venae cavae of dogs in supine position suggesting an inspiratory increase of the hepatic contribution to blood flow in IVC. Bradley (1963) suggested that external factors such as respiratory rate, position, body size, etc., would influence the interaction of hepatic outflow and respiration but this remained unproven. Therefore we investigated the influence of body position and of pneumoperitoneum on venous return by IVC, including hepatic outflow as well as renal outflow.

## Methods

18 dogs of either sex, weighing 17 to 28 kg, were anesthetized, after premedication by acepromazine 1 mg/kg, with intravenous chloralose-urethane (for induction 25–50 mg/kg and 125–250 mg/kg, and for maintenance 5–10 mg/kg/hr and 25–50 mg/kg/hr, respectively). Being ventilated via a cuffed endotracheal tube by a Harvard respiration pump (model 607) under muscular relaxation with diallyl-nor-toxiferine 100 μg/kg, the dog was positioned on the left side and the chest was opened on the right side in the 5th or 6th intercostal space to place Teflon rings around the superior vena cava (SVC) and the IVC close to the veno-atrial junction in order to maintain the venae cavae at a constant diameter. The Teflon ring was 10 or 12 mm wide and 20 mm long with a 4 mm thick wall; in the ring 3 X-ray opaque bars were imbedded along the axis. A 2 mm wide longitudinal slit in the wall allowed the insertion of the vena cava and could be closed by a plug flush with the inner surface of the Teflon ring. Then the chest wall was closed leaving a multiholed Nelaton catheter (no. 20 F) along the frontal mediastinum leading outside, where it was closed by a stopcock.

In the supine animal the IVC in the abdomen was equipped with Teflon rings just above and below the confluence of the renal veins, using a median laparotomy; the abdominal wall was closed. A Nelaton catheter (no. 20 F) was passed to the subphrenic space and the outside end was closed by a stopcock. Through these catheters the thoracic and abdominal cavities were evacuated by syringe suction. After these operations the dog was disconnected from the pump and left to breathe room air spontaneously. Blood pressure in the aorta and in the vena cava was measured by Statham strain gauges P23AA and P23Db via catheters introduced through branches of the left brachial artery and vein to the respective places. The zero pressure level was chosen at the height of the right atrium in supine position. The level of the right atrium was found by fluoroscopy. The left femoral artery and vein were catheterized with a blood-type catheter $P_{O_2}$ electrode (Kimmich and Kreuzer, 1969) and a catheter electromagnetic flow probe (Transflow 600; Skalar, Delft) to measure arterial $P_{O_2}$ in the aorta and blood velocity in the IVC respectively. To reach the SVC the flow probe was introduced from the right external jugular vein. Coagulation of blood was pre-

vented by heparin (2 ml of solution containing 5000 units/ml). Respiratory gas flow was recorded using a pneumotachograph, respiratory $P_{O_2}$ and $P_{CO_2}$ were monitored using a gas-type $P_{O_2}$ electrode (Schuler and Kreuzer, 1967) and an infrared $CO_2$ analyzer respectively. All quantities were recorded on a Honeywell Visicorder 1108.

After performing all the preparations blood velocity in the venae cavae was measured at the levels fixed by the Teflon rings. The catheter flow probe was simply shifted from one ring to the other under fluoroscopic control; the venous catheter was also moved so that the caval pressure was recorded simultaneously within $\pm$ 1 cm from the flow sensor. Then, still in supine position, the stopcock on the abdominal cavity catheter was opened so that a free communication between the abdominal cavity and the outside atmosphere was established. After waiting for 10 to 20 minutes to reach a new steady state indicated by arterial $P_{O_2}$ and respiratory $P_{O_2}$ and $P_{CO_2}$, flow and pressure measurements were repeated. The pneumoperitoneum was removed and vena cava flow was again observed. Thereafter the dog was positioned laterally either on the left side (12 dogs) or on the right side (2 dogs) and the measurements of caval venous pressure and flow were repeated after allowing 10 to 20 minutes for a new steady state to be reached. Prone position was also tested in 4 dogs before or after the lateral position. Finally, the dog was again placed in supine position and the last measurements of pressure and flow were performed. At the end of the experiment the animal was killed. The thoracic and abdominal cavities were inspected for bleeding; in no case severe bleeding possibly impairing circulation was found.

Hepatic and renal contributions to IVC were obtained by subtracting the flow rate recorded below the respective venous junctions from that above. For this purpose parts of the records obtained at the adjacent caval venous levels were chosen so that the tracings of pneumotachogram and arterial pressure were almost completely superimposed for more than two breathing cycles. Then from these parts of the records pneumotachogram, arterial pressure, venous pressure, and blood flow were traced on transparent paper; the vertical distance between two flow tracings on superposition of the records of adjacent caval venous levels was measured and plotted against an arbitrary zero line every 0.05 sec corresponding to the time scale of the record. When Teflon rings of different diameters were used at adjacent caval venous levels, the deflection of blood flow tracing on one of the records was corrected to show the same flow rate in the ring as with the other diameter according to calibration lines for equivalent situations obtained before.

The flow probe used in this study was similar to that of Mills (1966) but for the iron core. The outside diameter was 2 mm; there was no central lumen for pressure recording. The electrodes were situated about 4 cm from the tip. The flow sensing part was always kept in the middle of the Teflon ring by a spring wire holder fitted to the flow catheter on either side of the sensor; one side of the holder was mobile along the catheter (figure 1). This spring wire holder did not disturb the output of the flowmeter nor its zero point when tested in an in vitro pump system. The zero point in situ during the experiment was assumed to be the same as that obtained at the end of the experiment when the heart beat was stopped. The deviation of the zero point

in situ from that obtained in vitro in saline solution before the experiment did not exceed a blood flow of about 40 ml/min. The calibration of the flowmeter was performed in a roller pump system with adjustable flow rate and filled with canine blood. The flow probe was placed in the center of a glass tube by means of the spring wire holder; the diameter of the glass tube was either 10 mm or 12 mm corresponding to

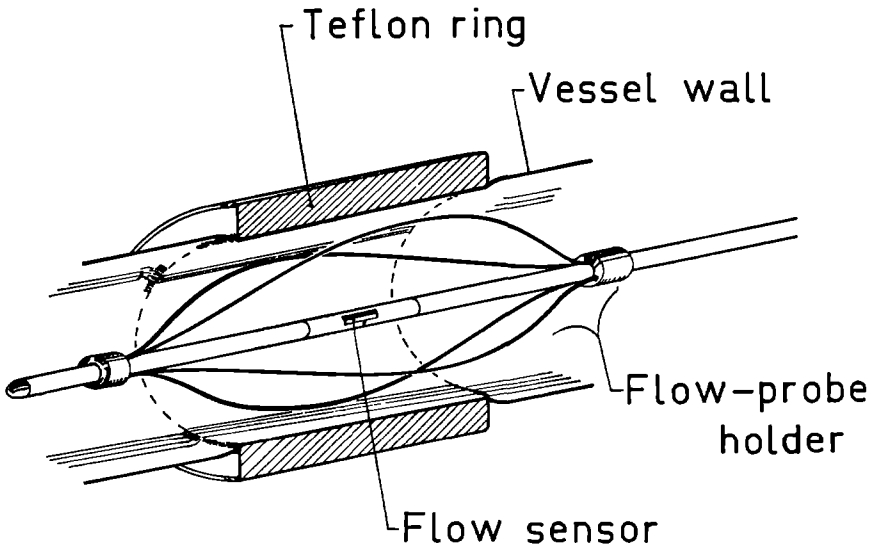



Fig. 1. Schematic representation of flow probe used. The flow sensor was always kept in the center of the Teflon ring-fixed level of the vena cava by a flow probe holder with 4 spring wires.

the size of the Teflon rings. The calibration line was prepared by plotting the deflection of mean flow against volume flow rate of the pump. The calibration was very stable and remained almost unchanged with several calibrations over 2 months. The influence of hematocrit was negligible between 38 % and 46 % but in blood of very low hematcrit (less than 20 %) or in saline the deflection obtained per unit flow was about 8 % greater.

Statistical significance of variations of pressure difference between the thoracic and abdominal vena cava was assessed by Student's t test taking $p = 0.05$ as limit.

## Results

Flow records in the venae cavae showed pulsatile variations with heart beat as well as with respiration. The variations were sometimes less marked in the abdomen than in the thorax. This paper deals with the respiratory variations only.

In supine position there was always a pronounced respiratory fluctuation of venous return in the thoracic IVC, independent of breathing frequency in the range of 10/min to 43/min. Figures 2 and 3 show flow variations with respiration at three levels of

the IVC and calculated hepatic and renal outflow in dogs breathing rapidly and slowly respectively. Flow patterns in the abdominal IVC were opposite to those in the thoracic IVC; there was a decrease or a trough during inspiration and an increase or a peak during expiration; abdominal caval venous flow patterns were quite similar at the levels above and below the renal veins. Only 3 out of 18 dogs had no inspiratory trough of vena cava flow above the renal veins and solely an increase towards the end of inspiration and the beginning of expiration. Hepatic outflow calculated as the difference of flow between thoracic and abdominal IVC increased during inspiration and decreased during expiration very markedly and the expiratory decrease often became even negative (figure 2). Renal outflow also showed respiratory variations in some dogs but far less than hepatic outflow and its relationship with respiratory

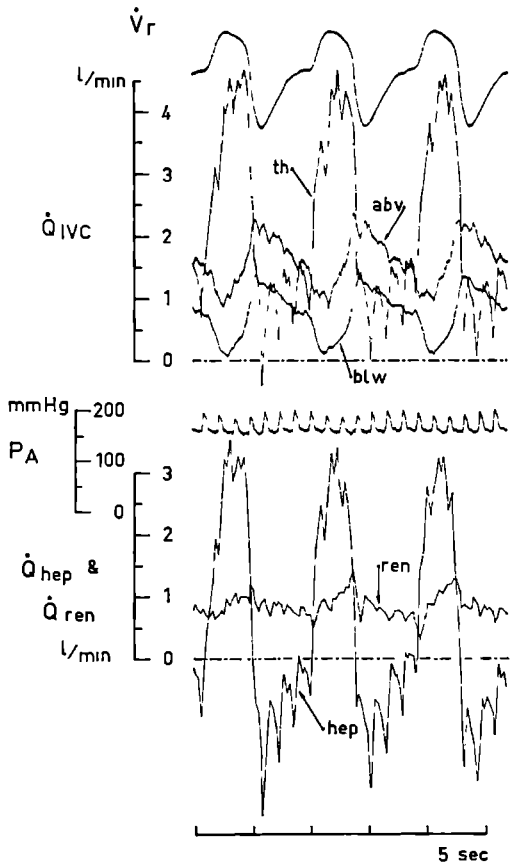



Fig. 2. Respiratory variation of blood flow in the inferior vena cava ($\dot{Q}_{IVC}$) and calculated hepatic and renal outflow in a dog (28 kg) in supine position. No pneumoperitoneum. Breathing frequency = 35/min. Tracings from top to bottom: pneumotachogram ($\dot{V}_r$) with inspiration upwards; inferior caval venous flow ($\dot{Q}_{IVC}$) in thorax (th), abdomen above renal veins (abv), and below renal veins (blw); arterial pressure ($P_A$); calculated hepatic and renal outflow ($\dot{Q}_{hep}$, $\dot{Q}_{ren}$). Note negative hepatic outflow during expiration.

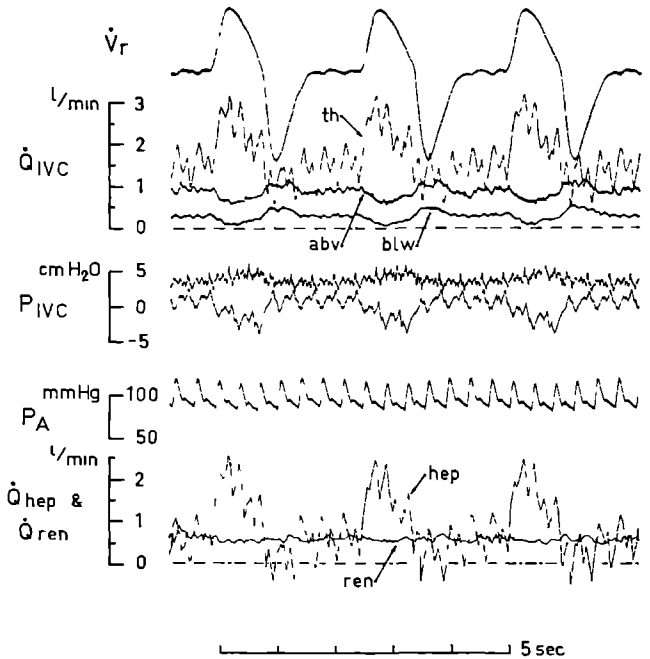



Fig. 3. Respiratory variation of blood flow in the inferior vena cava and calculated hepatic and renal outflow in a dog (20 kg) in supine position. No pneumoperitoneum. Breathing is slower than in figure 2 (23/min). Tracings from top to bottom: pneumotachogram ($\dot{V}_r$); inferior caval venous flow ($\dot{Q}_{IVC}$) in thorax (th), abdomen above renal veins (abv), and below renal veins (blw); inferior caval venous pressure ($P_{IVC}$) in the abdomen above renal veins and in the thorax (= right atrial pressure here); arterial pressure ($P_A$); calculated hepatic and renal outflow ($\dot{Q}_{hep}$, $\dot{Q}_{ren}$).

phase was not clear-cut; in other dogs there was almost no respiratory variation in renal outflow. Even with constant renal outflow (figure 3), however, the relative contribution of renal venous flow changed periodically due to the respiratory variations in IVC flow below the renal veins.

In 8 supine dogs the abdominal cavity was exposed to atmospheric pressure by opening the stopcock on the abdominal catheter. Fluoroscopic observation revealed that the diaphragm was elevated and the liver was situated more dorsal while air penetrated into the subphrenic and epigastric parts. At the same time there was a temporary increase of ventilation, predominantly through a higher respiratory rate. By this maneuver the inspiratory increase of venous return in the thoracic IVC was lowered in all dogs and more limited to the first half of the inspiratory period in 3 dogs (figure 4). The abdominal IVC flow shape did on the average not show any clear change from the air-free condition. The hepatic outflow pattern was not much changed, but the amplitude of inspiratory increase was reduced in all dogs (figure 4). The maneuver did not induce any important change in the caval venous pressure (figures 3 and 4) or in the preinspiratory pressure difference between thoracic and

abdominal vena cava ($p > 0.4$). After the pneumoperitoneum was eliminated the IVC flow was restored to the pattern observed previously.

Lateral position was examined in 14 dogs, 2 on the right side and 12 on the left side. After postural change on either side ventilation was temporarily increased, gradually returning to nearly the previous level. The flow pattern in the thoracic IVC

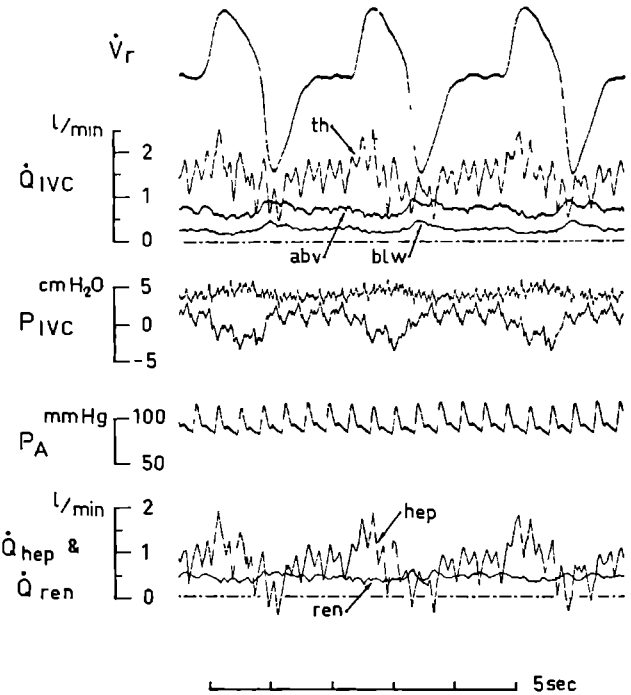



Fig. 4. Respiratory variation in inferior caval venous flow of the dog of figure 3, in supine position with pneumoperitoneum. Breathing frequency = 25/min. Tracings from top to bottom: pneumotachogram ($\dot{V}_r$); inferior vena cava flow ($\dot{Q}_{IVC}$) in thorax (th), abdomen above renal veins (abv), and below renal veins (blw); pressure in the inferior vena cava ($P_{IVC}$), above renal veins and in thorax; arterial pressure ($P_A$); calculated hepatic and renal outflow ($\dot{Q}_{hep}$, $\dot{Q}_{ren}$). Note that rate of the inspiratory increase of thoracic caval venous flow and hepatic outflow is less than in figure 3 while the flow pattern is not much changed and that the peak of inspiratory increase is shifted towards the beginning of inspiration.

changed markedly in 12 dogs and remained unchanged in 2 dogs. The most pronounced change in the flow pattern was a reversal of the respiratory variation; there was a decrease of venous return during inspiration and recovery during expiration (in 5 dogs), sometimes with a short time lag between the beginning of inspiration and the onset of decrease of venous return (figure 5). In 6 other dogs venous return in the thoracic IVC still showed an increase at the beginning of inspiration but thereafter decreased throughout the inspiration, making it look like a biphasic change (figure 6,

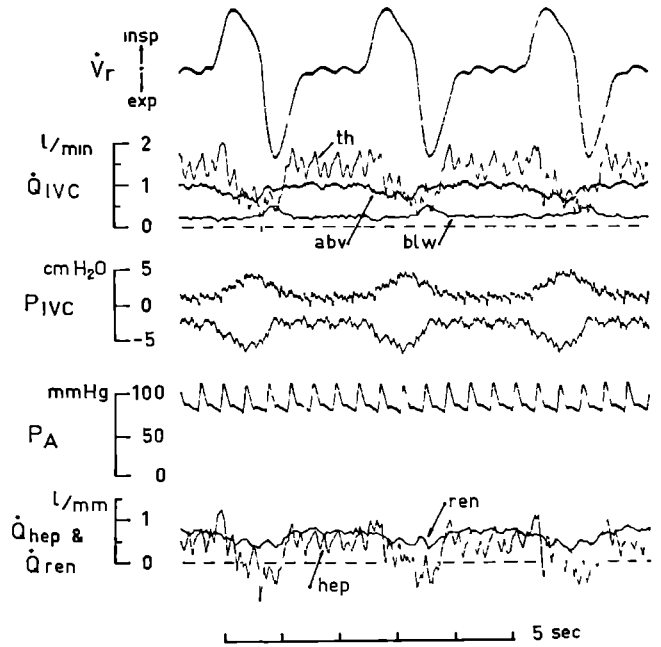



Fig. 5. Respiratory variation in inferior caval venous flow of the dog of figures 3 and 4, in left lateral position. Breathing frequency = 22/min. Tracings from top to bottom: pneumotachogram ($\dot{V}_r$); inferior vena cava flow ($\dot{Q}_{IVC}$) in thorax (th), abdomen above renal veins (abv), and below renal veins (blw); pressure in the inferior vena cava ($P_{IVC}$), above renal veins and in thorax; arterial pressure ($P_A$); calculated hepatic and renal outflow ($\dot{Q}_{hep}$, $\dot{Q}_{ren}$). In comparison with figure 3 the pressure difference between the thoracic and abdominal vena cava is increased and there is an inspiratory decrease of thoracic caval flow and hepatic outflow.

right panel). Breathing frequency (ranging from 19/min to 50/min) and the side of lateral position were of no importance.

The flow pattern in the abdominal IVC was also different from that in supine position; most frequently (12 dogs) there was above the renal veins a decrease during inspiration without the clear temporary overshooting increase during expiration as observed in supine dogs (compare figures 3 and 5, left and right panels in figure 6). In the other 2 dogs IVC flow remained unchanged. On the average there was no distinct difference in flow pattern between the abdominal IVC above and below the renal veins (figure 6) except 3 dogs in which a rather different IVC flow pattern was seen between these 2 levels (figures 3 and 5). Reflecting these variations of the flow pattern in thoracic and abdominal IVC, calculated hepatic outflow also showed several variation in detail. Generally, however, both the flow and its respiratory variation were larger in the thoracic IVC than in the abdomen; hepatic outflow displayed a pattern similar to that of the thoracic IVC, i. e., a predominant decrease during inspiration (figure 5, 6 dogs), a slight increase only at the beginning of inspiration

followed by a decrease (right panel of figure 6, 6 dogs), or no clear-cut respiratory variation (2 dogs).

Apart from these changes of flow pattern in the IVC in lateral position there was also a change in the preinspiratory pressure difference between the IVC in thorax and abdomen; it increased on the average from 2.0 $\pm$ 0.85 cm $H_2O$ (n = 18) in supine position to 5.3 $\pm$ 0.92 cm $H_2O$ (n = 14) in lateral position ($p < 0.001$). With the exception of 2 dogs there was a tendency to a predominant decrease of venous return

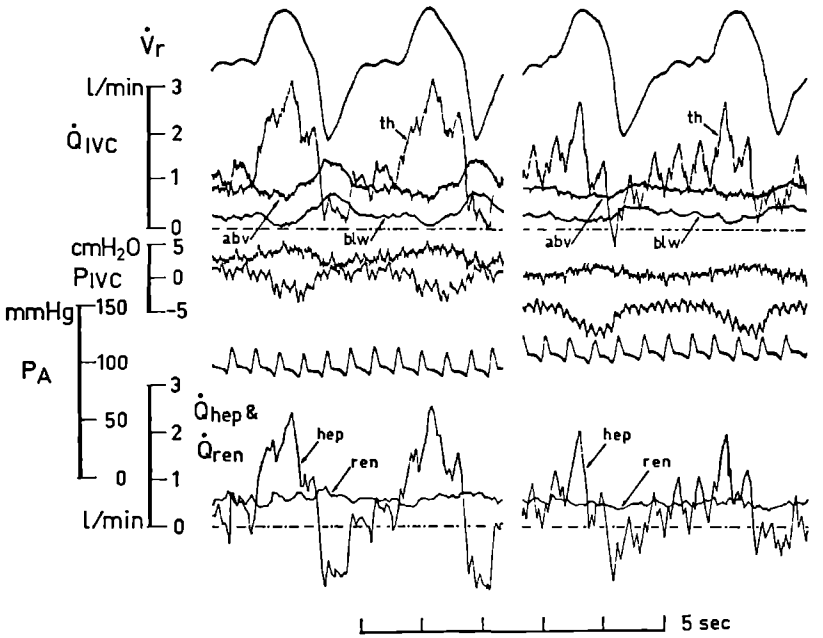



Fig. 6. Respiratory variation of inferior caval venous blood flow in a dog (26 kg) in supine position without pneumoperitoneum (left panel) and in left lateral position (right panel). Tracings from top to bottom: pneumotachogram ($\dot{V}_r$); inferior vena cava flow ($\dot{Q}_{IVC}$) in thorax (th), abdomen above renal veins (abv) and below renal veins (blw); inferior vena cava pressure ($P_{IVC}$) above renal veins and in thorax; arterial pressure ($P_A$); calculated hepatic and renal outflow ($\dot{Q}_{hep}$, $\dot{Q}_{ren}$). Note that thoracic IVC flow and hepatic outflow in lateral position (right panel) show a tendency to increase at the beginning of inspiration and to decrease during later inspiration; the rate of inspiratory increase is far less than in supine position (left panel).

in the IVC and of calculated hepatic outflow during inspiration in the dogs which developed a preinspiratory caval pressure difference in lateral position higher than 5 cm $H_2O$; dogs with less marked changes in venous return showed a smaller increase of their preinspiratory caval pressure difference. The stopcock on the abdominal catheter was opened in 7 dogs positioned laterally, but spontaneous suction of air was not seen except in 2 dogs, one of which showed an increase of caval pressure difference from 4.5 cm $H_2O$ to 7.5 cm $H_2O$ with a clear-cut decrease of thoracic IVC

flow during inspiration. Those dogs which did not show any spontaneous suction remained without further changes.

Prone position was examined in 4 dogs. The pattern of venous return in the IVC was more similar to that in lateral position than to that in supine position; the thoracic IVC flow showed a decrease during inspiration (2 dogs), a slight increase

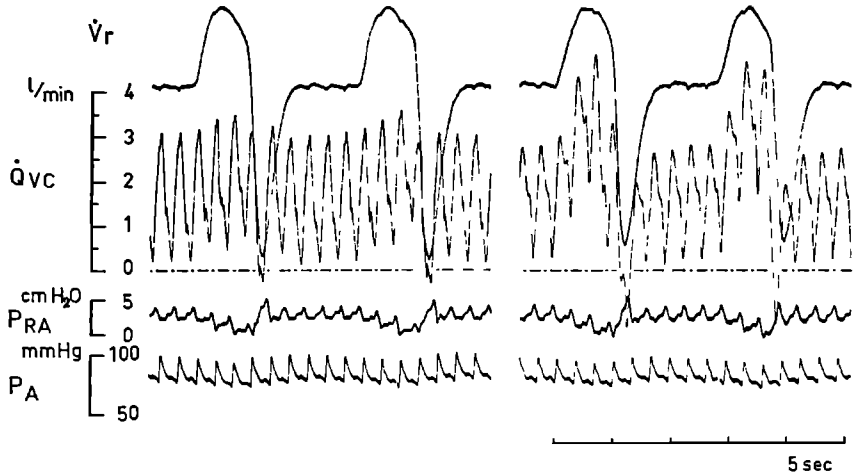



Fig. 7. Comparison of blood flow in inferior and superior venae cavae of a dog in supine position without pneumoperitoneum. Left panel shows SVC flow, right panel IVC flow. Tracings from top to bottom: pneumotachogram ($\dot{V}_T$); caval venous flow in thorax; right atrial pressure ($P_{RA}$); arterial pressure ($P_A$).

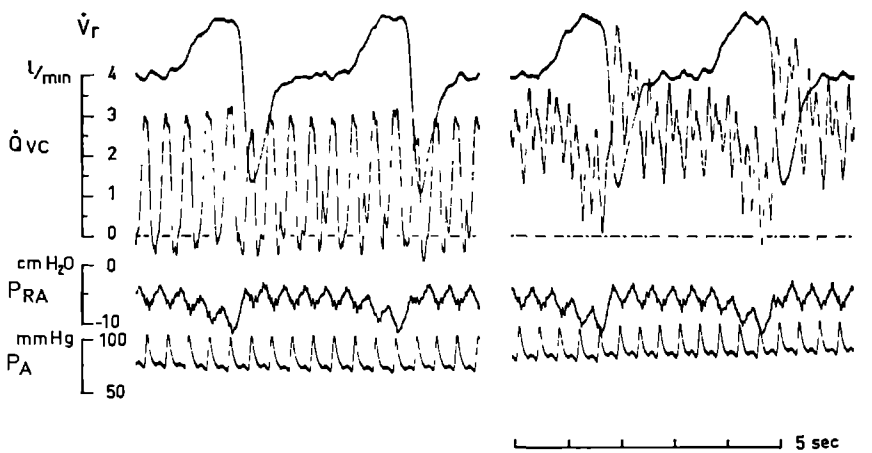



Fig. 8. Comparison of blood flow in inferior and superior venae cavae of the dog of figure 7, in left lateral position. Left panel shows SVC flow, right panel IVC flow. Tracings from top to bottom: pneumotachogram ($\dot{V}_T$); caval venous flow; right atrial pressure ($P_{RA}$); arterial pressure ($P_A$). Note that respiratory variation of inferior vena cava flow is completely reversed while that of superior vena cava flow remains almost unchanged.

only at the beginning of inspiration (1 dog), or no change from that in supine position (1 dog, in which there was also no change in lateral positon); abdominal IVC flow pattern was more similar to that in supine position (4 dogs). The preinspiratory caval pressure difference between thorax and abdomen was clearly higher than in supine position in all dogs ($6.5 \pm 0.81$ cm $H_2O$, $n = 4$, $p < 0.001$).

In 3 dogs the SVC and the IVC flow patterns were compared in supine position and in lateral position. The flow in the SVC increased during inspiration in both positions, though far less than in the IVC in supine position; since the IVC flow decreased in lateral position the venous return in the thoracic venae cavae differed in its direction of variation with respiration in lateral position (figures 7 and 8).

## Discussion

The catheter tip velocity probe introduced by Mills (1966) has been proven to be quite useful to explore velocity patterns along large vessels by moving it back and forth (Wexler *et al.*, 1968; Mills *et al.*, 1970), even though the velocity signal obtained by the probe sensor represents only that within 2 mm of the catheter rather than the mean velocity in the cross sectional area of a vessel as in the case of cuff-type flow probes (Mills and Shillingford, 1967). When comparing the output of the catheter velocity probe with that of a cuff-type probe (Skalar, Delft) in a dog we found that they agreed quite well in pulsatile and respiratory variations and thus were suited for our purpose. In the application of a catheter tip velocity probe Wexler *et al.* (1968) and Mills *et al.* (1970) assumed that the velocity profile in venae cavae and aorta is flat; they did not mention the problem of the position of the flow sensor in the cross sectional area of the vessel. However, we were often bothered by a shift of the flow record after the velocity probe was removed and reinserted to the same level of a vessel, even though such a displacement could be corrected for by manipulating the probe catheter. Also in a pulsatile pump system we observed that the flow signal changed when the probe sensor approached the tube wall and even crossed the zero line when the sensor was almost touching the wall. To be sure that the probe sensor was really far enough from the vessel wall we applied the probe holder shown in figure 1 and thus obtained a more stable flow recording.

Since the application of both the conventional cuff-type flow probe and of our technique requires a close cuff-to-vein contact, collapsibility of the vessel should be considered particularly in acute experiments. Our Teflon rings always fitted snugly or constricted slightly throughout the cardiac and respiratory cycle under atmospheric pressure. This ensures a better contact between the venae cavae and the Teflon rings after chest and abdomen were closed because there is a shrinkage of heart and central vessels under open-chest condition (Rushmer and Smith, 1959). Moreover the caval venous wall was fixed against the Teflon ring by the flow probe holder. The question arises whether the constriction of the venae cavae by the Teflon rings influences the flow pattern. According to Spencer and Denison (1959) arterial circumference can be constricted by 20 % without distortion of flow pattern. When applying this observa-

tion to the venous side, we do not know how far the venae cavae were narrowed by the Teflon rings at the time of measurement. However, we believe that there should occur no serious distortion of vena cava flow pattern because we never saw any measurable pressure difference in the vena cava between just above and below the Teflon rings and the flow patterns in the venae cavae of supine dogs obtained in preliminary experiments without Teflon rings were principally the same as observed in this study.

The flow patterns obtained in the thoracic IVC in supine position with or without pneumoperitoneum are quite comparable with those obtained by Mixter (1953) and Attinger *et al.* (1967) in anesthetized dogs as well as by Morgan *et al.* (1966a and b) and Abel and Waldhausen (1968a en b) in conscious dogs. Also abdominal caval flow was mostly similar to that found by Mixter (1953); 3 dogs showed no decrease during inspiration but rather an increase later during inspiration similar to the results of Moreno *et al.* (1967). Hepatic outflow calculated as the difference of inferior vena cava flow between the thorax and above the renal veins always showed an increase during inspiration (figures 2 and 3). Strictly speaking it might not be correct, however, to interpret this calculated caval flow difference directly and entirely as hepatic outflow since a volume change of the IVC segment in the thorax and beneath the diaphragm but not below the liver was demonstrated by Norhagen (1963) during the respiratory cycle, i. e., the IVC segment in the thorax was extended along its longitudinal axis without change of diameter and the segment below the diaphragm was narrowed during inspiration. Therefore the blood shift due to the volume change of the IVC segment between the thoracic and abdominal Teflon rings during the respiratory cycle is also included in the calculated hepatic outflow. We did not take, however, this volume change of the IVC segment into account for the calculation of hepatic outflow because of its minor importance. During early expiration there was often a negative hepatic outflow (figures 2 and 6) which corresponds quite well with a reflux of contrast medium into the hepatic veins from the vena cava during early expiration as demonstrated by Norhagen (1963).

On the other hand renal outflow was less influenced by respiration than hepatic outflow and often respiratory variation was barely visible. Even when there was some respiratory variation it was variable from dog to dog and we could not find any clear-cut relationship between renal outflow and respiratory phase. However, the contribution of the renal veins to the abdominal vena cava showed cyclic variation in each dog because of the respiratory variation in the vena cava flow below the renal veins which was even negative during inspiration in some cases. These findings concerning hepatic and renal outflow in supine dogs agree quite well with the respiratory variation of caval venous oxygen pressure as reported by Yokota and Kreuzer (1972).

Exposure of the abdominal cavity to atmospheric pressure did not change the basic pattern of venous return in the IVC. Nevertheless the inspiratory increase of the thoracic IVC flow and therefore that of the hepatic outflow diminished in all animals. Since the pressure pattern and the preinspiratory difference of caval venous pressure between thorax and abdomen remained unchanged, it cannot be the result of a direct

hemodynamic change of the vena cava. On the other hand it was observed that a large subphrenic space was formed with suction of air into the abdominal cavity and that contact between diaphragm and liver was lost. In such a conditon squeezing of blood from visceral organs to the vena cava by descent of the diaphragm or by increase of abdominal pressure (Hales, 1733, quoted by Franklin, 1937; Franklin, 1937; Eckstein *et al.*, 1947; Alexander, 1951; Brecher, 1956) will be reduced. Or else, loss of spatial support of the liver together with deformation of the soft liver tissue due to positional change might reduce the blood content in the hepatic veins; less blood would be available to flow into the IVC during the inspiratory increase of caval venous pressure difference between thorax and abdomen.

The increase of SVC flow during inspiration in supine dogs mentioned by Brecher and Mixter (1953) was also observed in this study even though the respiratory variation of blood flow was less marked in the SVC than in the thoracic IVC as reported by Abel and Waldhausen (1968b), and the pattern of the SVC flow remained almost unchanged after the dog was positioned laterally. To the contrary the thoracic IVC flow pattern was markedly influenced by the change of posture; the most conspicuous feature of the thoracic IVC flow pattern of dogs positioned laterally was a decrease during inspiration instead of an increase in supine position. This reversal of inspiratory change of flow in the thoracic IVC in lateral position was rather unexpected because it has been widely believed since Mixter (1953) and Brecher and Mixter (1953) that inspiration increases venous return both in the IVC and SVC, at least during quiet breathing. It might be worth mentioning that the original experiments by these authors were conducted in supine dogs; subsequently, several reports have appeared concerning venous return such as by Brecher and Hubay (1955), Brawley *et al.* (1966), Pinkerson *et al.* (1966), Attinger *et al.* (1967), Moreno *et al.* (1967) in anesthetized dogs, and Morgan *et al.* (1966a and b), Tafur and Guntheroth (1966) as well as Abel and Waldhausen (1968a and b) in conscious dogs, but we could not find any report on flow in the thoracic IVC in a clearly defined lateral position during spontaneous breathing. Our finding of a reversed pattern of the thoracic IVC flow cannot be the result of the abdominal operation since we have seen this phenomenon also in 2 dogs whose abdomen was not operated on. Also breathing frequency does not seem to affect this finding.

It should be noted that the change of respiratory variation of venous return was accompanied by an increase of the preinspiratory pressure difference in the IVC between thorax and abdomen. It is not clear from our measurements of venous pressure whether this increase of the pressure difference was due to lowering of the thoracic IVC pressure or to increase of the abdominal caval pressure, because we did not readjust the height of the pressure transducer to the altered level of the right atrium after the dog was changed to lateral position. Therefore we measured pleural pressure in 2 dogs and saw a change of 1.5 to 2.5 cm $H_2O$ between supine and lateral positions. Such a change, however, would be negligible for the vena cava if we consider the distance between the place of pleural pressure measurement and the vena cava as well as the vertical pleural pressure gradient (Hoppin *et al.*, 1969; McMahon

*et al.*, 1969). This might suggest that the increase of the caval venous pressure difference is of abdominal origin. This might also explain that the SVC flow pattern was not influenced by the change of position while the respiratory IVC flow pattern was reversed. Abdominal pressure must have been higher in lateral than in supine position since spontaneous suction of air into the abdominal cavity did not occur in lateral position. Such a change of abdominal pressure might be attributed to the influence of the shape of the canine thoracic cage on the abdominal cavity, the sagittal axis of the thorax being longer than the frontal one in most dogs; since therefore the abdominal wall would be less collapsible in supine position, abdominal pressure should be higher in lateral position.

The caval pressure difference between thorax and abdomen was explained as a hydraulic pressure gradient caused by 2 separate and different pressure systems on a collapsible tube according to Duomarco and Rimini (1954) and was demonstrated to increase parallal to abdominal pressure by Guyton and Adkins (1954). More recently Doppman *et al.* (1966) showed radiologically that with increase of abdominal pressure narrowing or collapse of the IVC occurred at the infradiaphragmatic portion although they did not mention the exact degree of pressure increase. Thus our finding of a reversed pattern of respiratory variation in the thoracic IVC flow in lateral position could be explained by the increased abdominal pressure favoring collapse of IVC just below the diaphragm and thus affecting hepatic outflow and raising the caval pressure difference. The increase of abdominal pressure required for a temporary collapse of the IVC during inspiration would be rather small since the thoracic IVC flow pattern with respiration was reversed in most dogs whose preinspiratory caval pressure difference between thorax and abdomen was only slightly above 5 cm $H_2O$.

According to findings in conscious dogs by Morgan *et al.* (1966a), and Abel and Waldhausen (1968b), it was presumed that vena cava flow and hepatic outflow patterns in prone position would not be different from those in supine position. Our findings on four dogs, however, were rather similar to those in lateral position and the vena cava pressure difference between thorax and abdomen was significantly higher than in supine position. There is a marked difference between anesthetized and conscious dogs, even in the same prone position, in the supporting points of the body, i. e., anesthetized dogs are lying on thorax and abdomen whereas conscious dogs still maintain their bodily support by the joints of shoulder and hip. Compression of the frontal abdominal wall by the body weight would lead to an increase of abdominal pressure the influence of which on the IVC flow pattern is discussed above for dogs in lateral position.

It has been pointed out repeatedly that IVC flow and hepatic outflow are influenced by many factors (Franklin, 1937; Brecher, 1956; Bradley, 1963). The suggestion of the last author that the discrepancy in the opinions concerning the respiratory variation of hepatic outflow could be attributed to external factors is substantiated by our study; a simple change in the position of the experimental subjects can lead to completely different findings. Still we cannot be sure that the contradictory views concerning hepatic outflow are completely explained by differences in position only. In some reports the experimental conditions are not precisely mentioned. As far as

venous flow is concerned the main conclusion of these experiments is that the experimental condition must be defined exactly because venous pressure is easily influenced by apparently trivial differences as shown here.

## References


Abel, F. L. and J. A. Waldhausen (1968a). Effects of anesthesia and artificial ventilation on caval flow and cardiac output. *J. Appl. Physiol.* 25: 479–484.

Abel, F. L. and J. A. Waldhausen (1968b). Influence of posture and passive tilting on venous return and cardiac output. *Am. J. Physiol.* 215: 1058–1066.

Alexander, R. S. (1951). Influence of the diaphragm upon portal blood flow and venous return. *Am. J. Physiol.* 167: 738–748.

Attinger, E. O., H. Sugawara, A. Navarro, T. Mikami, and R. Martin (1967). Flowpatterns in the peripheral circulation of the anesthetized dog. *Angiologica* 4: 1–27.

Bradley, S. E. (1963). The hepatic circulation. In: Handbook of Physiology. Section 2: Circulation. Vol. II, edited by W. F. Hamilton and P. Dow. Washington, D. C., American Physiological Society, pp. 1387–1438.

Brauer, R. W., R. F. McElroy, Jr. and G. F. Leong (1960). Blood flow in the hepatic veins of the rat. *Physiologist* 3(3): 28.

Brawley, R. K., H. N. Oldham, J. S. Vasko, R. P. Henney, and A. G. Morrow (1966). Influence of right atrial pressure pulse on instantaneous vena caval blood flow. *Am. J. Physiol.* 211: 347–353.

Brecher, G. A. (1956). Venous Return. New York, Grune & Stratton.

Brecher, G. A. and G. Mixter, Jr. (1953). Effect of respiratory movements on superior cava flow under normal and abnormal conditions. *Am. J. Physiol.* 172: 457–641

Brecher, G. A. and C. A. Hubay (1955). Pulmonary blood flow and venous return during spontaneous respiration. *Circulation Res.* 3: 210–214.

Doppman, J., R. M. Rubinson, S. D. Rockoff, J. S. Vasko, R. Shapiro, and A. G. Morrow (1966). Mechanism of obstruction of the infradiaphragmatic portion of the inferior vena cava in the presence of increased intra-abdominal pressure. *Invest. Radiol.* 1: 37–53.

Duomarco, J. L. and R. Rimini (1954). Energy and hydraulic gradients along systemic veins. *Am. J. Physiol.* 178: 215–220.

Eckstein, R. W., C. J. Wiggers and G. R. Graham (1947). Phasic changes in inferior cava flow of intravascular origin. *Am. J. Physiol.* 148: 740–744.

Franklin, K. J. (1937). A Monograph on Veins. Springfield, Illinois, Charles C Thomas.

Grabner, G. (1963). Einige methodische, pathophysiologische und klinische Probleme des enterohepatalen Kreislaufes. *Wien. Z. Inn. Med.* 44: 221–305.

Guyton, A. C. and L. H. Adkins (1954). Quantitative aspects of the collapse factor in relation to venous return. *Am. J. Physiol.* 177: 523–527.

Hoppin, F. G., Jr., I. D. Green and J. Mead (1969). Distribution of pleural surface pressure in dogs. *J. Appl. Physiol.* 27: 863–873.

Kimmich, H. P. and F. Kreuzer (1969). Catheter $P_{O_2}$ electrode with low flow dependency and fast response. In: Oxygen Pressure Recording in Gases, Fluids and Tissues, edited by F. Kreuzer. Progr. in Resp. Res. Vol. 3, edited by H. Herzog. Basel, Karger, pp. 100–110.

McMahon, S. M., D. F. Proctor and S. Permutt (1969). Pleural surface pressure in dogs. *J. Appl. Physiol.* 27: 881–885.

Mills, C. J. (1966). A catheter tip electromagnetic velocity probe. Phys. in Med. Biol. 2: 323–324.

Mills, C. J. and J. P. Shillingford (1967). A catheter tip electromagnetic velocity probe and its evaluation. *Cardiovascular Res.* 1: 263–273.

Mills, C. J., I. T. Gabe, J. H. Gault, D. T. Mason, J. Ross, Jr., E. Braunwald, and J. P. Shillingford (1970). Pressure-flow relationships and vascular impedance in man. *Cardiovascular Res.* 4: 405–417.

Mixter, G., Jr. (1953). Respiratory augmentation of inferior vena caval flow demonstrated by a low-resistance phasic flowmeter. *Am. J. Physiol.* 172: 446–456.

Moreno, A. H. (1964). Perpetuation of cirrhotic ascites as a result of altered regulation of venous return. *Bull. N. Y. Acad. Med.* 40: 80.

Moreno, A. H., A. R. Burchell, R. van der Woude, and J. H. Burke (1967). Respiratory regulation of splanchnic and systemic venous return. *Am. J. Physiol.* 213: 455–465.

Morgan, B. C., F. L. Abel, G. L. Mullins, and W. G. Guntheroth (1966a). Flow patterns in cavae, pulmonary artery, pulmonary vein, and aorta in intact dogs. *Am. J. Physiol.* 210: 903–909.

Morgan, B. C., D. H. Dillard and W. G. Guntheroth (1966b). Effect of cardiac and respiratory cycle on pulmonary vein flow, pressure, and diameter. *J. Appl. Physiol.* 21: 1276–1280.

Neumayr, A. A. (1964). Problems of the hepatic circulation in health and disease. *Gastroenterology* 47: 343–353.

Norhagen, A. (1963). Selective angiography of the hepatic veins. *Acta Radiol., Suppl.* 221: 1–121.

Pinkerson, A. L., M. H. Luria and E. D. Freis (1966). Effect of cardiac rhythm on vena caval blood flows. *Am. J. Physiol.* 210: 505–508.

Rushmer, R. F. and O. A. Smith, Jr. (1959). Cardiac control. *Physiol. Rev.* 39: 41–68.

Schuler, R. and F. Kreuzer (1967). Rapid polarographic in vivo oxygen catheter electrodes. *Respir. Physiol.* 3: 90–110.

Selkurt, E. E. and G. A. Brecher (1956). Splanchnic hemodynamics and oxygen utilization during hemorrhagic shock in the dog. *Circulation Res.* 4: 693–704.

Spencer, M. P. and A. B. Denison, Jr. (1959). The square-wave electromagnetic flowmeter: theory of operation and design of magnetic probes for clinical and experimental application. *IRE Trans. Med. Electron.* 6: 220–228.

Tafur, E. and W. G. Guntheroth (1966). Simultaneous pressure, flow and diameter of the vena cava with fright and exercise. *Circulation Res.* 19: 42–50.

Wexler, L., D. H. Bergel, I. T. Gabe, G. S. Makin, and C. J. Mills (1968). Velocity of blood flow in normal human venae cavae. *Circulation Res.* 23: 349–359.

Yokota, H. and F. Kreuzer (1972). Respiratory fluctuations of oxygen tension in central venous blood of anesthetized dogs. *Respir. Physiol.* 15: 350–364.

## *Discussion*

The lung model used by all investigators for the calculation of the time course of $P_{AO_2}$ throughout the respiratory cycle was very simple, consisting of a common airway and one or two 'alveoli'. Ventilatory and blood flow patterns during a respiratory cycle were arbitrarily chosen by the individual investigators, and differed as shown in Table 1. Since the purpose of our calculation of $P_{AO_2}$ was to compare its magnitude with that of $Pa_{O_2}$ in animal experiments, it was necessary to alter the ventilatory pattern while simplifying the other factors as much as possible; for example, $\dot{V}_{O_2}$ was assumed to be constant. The assumption of constant $\dot{V}_{O_2}$ is different from that of constant blood flow implying constant $P\bar{v}_{O_2}$ where $\dot{V}_{O_2}$ is calculated from $P\bar{v}_{O_2}$, blood flow, dissociation curve, and alveolar ventilation. Only in the lung model with defined blood flow the difference of mean $P_{O_2}$ and $P_{CO_2}$ between alveoli and endcapillary blood could be investigated as done by Suwa and Bendixen (1972). However, determination of capillary blood flow variation throughout the respiratory cycle is not easy whereas $\dot{V}_{O_2}$ is one of the most easily measurable factors; furthermore by using $\dot{V}_{O_2}$ directly we can neglect blood flow, contact time, dissociation curve, or $P\bar{v}_{O_2}$. Actually in normoxia or in hyperoxia the assumption of constant blood flow gives almost constant $\dot{V}_{O_2}$ as shown by Nye (1970) and Hlastala (1972) for normoxia. In hypoxia,

TABLE 1

Comparison of lung models.

| Reference | Number of Alveolar Compartments | Ventilatory Pattern | Lung Perfusion |
|---|---|---|---|
| Chilton et al. (1954) | 1 & 2 | triangular | constant flow |
| Flumerfelt & Crandall (1968) | 1 | sinusoidal | variable with heart beat |
| Nye (1970) | 1 | any one acceptable | constant flow |
| Hlastala (1972) | 1 | any one acceptable | variable with heart beat |
| Suwa & Bendixen (1972) | 1 | sinusoidal | sinusoidal, variable with ventilation |
| Yokota et al. (1973) | 2 | any one acceptable | constant or sinusoidal $\dot{V}_{O_2}$ |

Reports concerning $CO_2$ only are not included here. Difference between flow- and $\dot{V}_{O_2}$-defined models is discussed in text.

however, constant blood flow does not give the same results as constant $\dot{V}_{O_2}$ because the alveolar-endcapillary $P_{O_2}$ difference is dependent on alveolar $P_{O_2}$ level (Lilienthal *et al.* 1946) and therefore $\dot{V}_{O_2}$ is also dependent on the variation of $P_{AO_2}$.

The behavior of pulmonary arterial flow with respiration depends on the ventilatory regime, i.e., it increases during inspiration and decreases during expiration with spontaneous breathing and inversely with positive pressure ventilation (references in chapter I). As a result of such a flow variation in the pulmonary artery, capillary blood flow also changes during the respiratory cycle though rather inconsistently from subject to subject (DuBois and Marshall, 1957), also depending on posture (Vermeire and Butler, 1968). Furthermore capillary blood flow shows pulsatile variation with the heart beat as demonstrated by Lee and DuBois (1955) and numerous other investigators (Wasserman and Comroe, 1962; Linderholm *et al.*, 1962; Bosman *et al.*, 1964 and 1965; Wasserman *et al.*, 1966; Karatzas and Lee, 1969 and 1970; Kaplan and Kimbal, 1970). Besides, $P\bar{v}_{O_2}$ changes during the respiratory cycle too, but it cannot be assessed yet how it would change at the entrance to the capillaries in connection with respiration. The influence of $\dot{V}_{O_2}$ variation on the time course of $P_{AO_2}$ was discussed already in chapter I; the influence of pulsatile capillary flow on $P_{AO_2}$ does not change our results according to Hlastala (1972).

As a consequence of tidal ventilation in a lung model, mean $P_{O_2}$ in the perfused

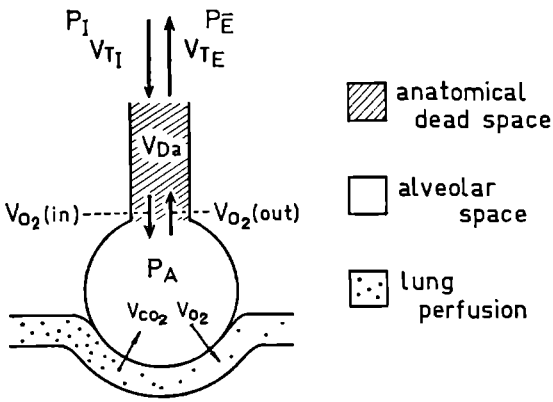



Fig. 1. Lung model with single alveoaler space. All symbols are the same as those in chapter I. For details see text.

alveolar space was proven to be lower than $P_{Ai_{O_2}}$ obtained by the conventional alveolar air equation. Suwa and Bendixen (1972) attributed this difference to reinspiration of dead space gas at the beginning of inspiration in their single alveolar model, whereas we showed in the discussion of chapter I that the difference was not due to the inhalation of dead space gas nor to a difference of alveolar ventilation in the two-alveolar lung model. It may be of some interest, then, to see what might be the result of reinspiration of dead space gas in the steady-state lung model with a single

alveolus since in the conventional lung model the alveolar space is ventilated only by ($V_T - V_{Da}$) of fresh air, neglecting reinpiration of dead space gas. In a lung model as in figure 1 the antomical dead space volume may be defined by Bohr's equation:

$$\frac{V_{Da}}{V_{TE}} = \frac{F_{ACO2} - \bar{F}_{EOC2}}{F_{ACO2}} \tag{1}$$

In a steady-state lung model the dead space gas composition should be the same as the alveolar gas after expiration. During the following inspiration the alveolar volume is increased by $V_{TI}$ in which the amount of $O_2$ is:

$$V_{O2}\,(in) = (V_{TI} - V_{Da})\,F_{IO2} + V_{Da} \,.\, F_{AO2} \tag{2}$$

The amount of $O_2$ leaving the alveolar space during expiration is:

$$V_{O2}\,(out) = V_{TE} \,.\, F_{AO2} \tag{3}$$

$O_2$ uptake and $CO_2$ output per breath are represented by $V_{O2}$ and $V_{CO2}$, respectively, where:

$$V_{TI} - V_{TE} = V_{O2} - V_{CO2} \tag{4}$$

The difference of $V_{O2}$ (in) and $V_{O2}$ (out) is $V_{O2}$, therefore from (2) and (3):

$$V_{O2} = (V_{TI} - V_{Da})\,F_{IO2} + V_{Da} \,.\, F_{AO2} - V_{TE} \,.\, F_{AO2} \tag{5}$$

Replacing $V_{TI}$ and $V_{Da}$ by (1) and (4), solving for $F_{AO2}$, and converting into partial pressure, we get:

$$P_{AO2} = P_{IO2} - \frac{V_{O2}}{X}\,[(P_B - P_{H2O}) + P_{IO2}\,(1 - R)] \tag{6}$$

where X is $V_{TE} \,.\, \bar{F}_{ECO2}/F_{ACO2}$ and corresponds to $\dot{V}_A$, the conventional alveolar ventilation; that is to say, equation (6) is equivalent to that given by Otis (1964). Therefore in a single alveolar model, if the ventilatory pattern is not taken into account, dead space gas reinspiration is not at all as important as in the two-alveolar lung model of chapter I. The term 'alveolar ventilation' is somewhat misleading in the sense that it does not mean the volume of gas itself which goes into the alveolar space and causes alveolar volume change, but that it is defined by ($V_T - V_D$) which implies only the fresh air entering the alveolar space. Thus 'alveolar ventilation' is a functional portion of total alveolar ventilation and when actual volume change of alveolar space is to be considered, total alveolar ventilation should be taken rather than 'alveolar ventilation'.

There is also a difference in the definition of mean alveolar $P_{O_2}$ between our approach and that of Suwa and Bendixen (1972); these authors used for mean $P_{A_{O_2}}$ the term $\frac{\int P_A \cdot \dot{V}_{A_E} \cdot dt}{\int \dot{V}_{A_E} \cdot dt}$ (integrated for the expiratory phase) whereas our term is $\frac{\int P_A \cdot dt}{\int dt}$, averaged only for the time throughout the respiratory cycle. Such a difference may result in a different $P_{A_{O_2}}$ even for the same situation. The difference of definition might be due to a different point of interest; we considered that the most important factor in determining endcapillary $P_{O_2}$ should be the alveolar $P_{O_2}$ in contact with capillary blood, and not the alveolar expirate. The expiratory flow-weighted mean $P_{O_2}$ of Suwa and Bendixen is the mean $P_{O_2}$ of the alveolar expirate and does not include the inspiratory side where the lowest $P_{A_{O_2}}$ is usually seen.

All of the lung models adopted for calculation of moment-to-moment variation of alveolar gases, including ours, were based on the assumption of a constant anatomical dead space throughout the respiratory cycle. The anatomical dead space, however, changes with lung volume by 2 to 3 % of lung volume change in man (Fowler, 1948; Shepard *et al.*, 1957; Birath, 1959). If we apply these figures to our animal experiments where $V_T$ was about 400 to 500 ml, the increase of anatomical dead space could be 8 to 15 ml. In fact the increase of anatomical dead space is not linearly related to that of lung volume, therefore this is a rough approximation only. Considering that the anatomical dead space measured by Fowler's method would correspond to end-inspiratory volume of dead space while neglecting gaseous diffusion between alveoli and airway, the anatomical dead space value at the beginning of inspiration should be smaller by 8 to 15 ml. The anatomical dead space value from Bohr's equation, if any exact value for mean total $P_{A_{CO_2}}$ were obtainable, must be the same as that from Fowler's method. Thus strictly speaking the anatomical dead space gas volume to be reinspired should be a little smaller than the anatomical dead space value measured during expiration. On the other hand it is well known that anatomical dead space decreases with elongation of inspiratory time or with breath holding due to gaseous diffusion between alveoli and airway. In our experiments inspiration by the pump ranged from 1.9 to 2.5 sec which is long enough to involve a decrease of dead space according to Fowler (1948). Therefore taking into account the difference in end-inspiratory and endexpiratory dead space volume could not be expected to improve the precision of the calculation of the time course of alveolar gases.

We also assumed, like the other authors, that gaseous diffusion in each lung compartment is instantaneous. However, Krogh and Lindhard (1914, 1917) emphasized that gaseous diffusion was important in mixing of inspired gases with air already present in the alveoli. Rauwerda (1946) calculated the time necessary for diffusion of

gases in a lung model and concluded that equilibrium in the alveolar space occurred rather fast, and that stratified inhomogeneity might be neglected. In 1966 Cumming *et al.* calculated the diffusion in the airways in a model with a diffusion distance larger than that of Rauwerda (1948), and found that an appreciable diffusion gradient persisted for as long as 5 sec or more. La Force and Lewis (1970) also calculated the diffusion time in the airways using a dichotomous airway with an established gaseous front and found a shorter equilibration time (1–2 sec) than Cumming *et al.* (1966). Cumming *et al.* (1971) investigated this problem further with a variable gas front in a dichotomous lung model and concluded that equilibrium in airway gas would not be reached during one physiological breathing cycle. Apart from purely theoretical and mathematical considerations Altshuler *et al.* (1959) and Muir (1967) showed by inhalation of aerosol with very low diffusion coefficient that respiration did not succeed to mix inspired gas mechanically with alveolar air by more than 15 % to 20 % of inspired gas. In 1965 Georg *et al.* have shown that the differences of diffusion velocity were demonstrable even in the normal lung for $SF_6$, Ne, and $H_2$. Cumming *et al.* (1967) also showed that the concentration of tracer gases, $SF_6$ and Ne, in alveolar samples continued to change during 30 sec of breath holding. Furthermore Power (1969) reported that variation of tracer gases in alveolar samples depended on tidal volume and, beyond a certain tidal volume distribution of $H_2$ and $SF_6$ in alveolar gas, did not differ any more; that is to say, when tidal volume is large enough, the difference of diffusion velocity is not very important. In a model study on gas transport Saidel *et al.* (1971) reported that for a sufficiently large tidal volume in relation to FRC, i.e., greater than 40 % of FRC, the limiting factor for gas transport was diffusion from alveoli to capillaries. From these reports it seems difficult to predict the influence of delayed diffusion equilibration on pericapillary $P_{O_2}$ in the alveolar space, and to assess the error due to the assumption of instantaneous diffusion. In our case, however, the error due to assuming instantaneous equilibration should be minimal according to Saidel (1971) and Power (1969) since we applied a rather large tidal volume of nearly 40 % to 50 % of FRC in our experiments.

In his investigation of the cyclic character of arterial oxygenation with oximetry in open chest dogs, Bergman (1961) did not dare to relate it to the pattern of $P_{A_{O_2}}$ as he was aware of the deformation due to the oximeter catheter-cuvette system. There is a limitation in showing arterial variation of oxygenation by oximetry, since the investigation should be confined to hypoxic condition due to the shape of the dissociation curve. Therefore Namur *et al.* (1961) studied cyclic variation of arterial $O_2$ saturation in man in hypoxic condition. When studying $Pa_{O_2}$ fluctuations synchronous with respiration by a $P_{O_2}$ micro-electrode incorporated into a flow-through cuvette, Purves (1966) found that the amplitude of respiratory $Pa_{O_2}$ fluctuations increased with higher $Pa_{O_2}$; we (Yokota and Kreuzer, 1970) also observed that the amplitude of $Pa_{O_2}$ fluctuation was slightly smaller in hypoxia than in normoxia in dogs breathing spontaneously (figure 2), but this difference in the amplitude of $Pa_{O_2}$ fluctuation was rather dubious in artificial ventilation (figure 3). According to Flumerfelt and Crandall (1968) and Hlastala (1972) the amplitude of $P_{A_{O_2}}$ fluctuation

due to respiration is the same in hypoxia and in normoxia, and the latter author also showed that the amplitude of $P_{O_2}$ fluctuation in the endcapillary blood in hypoxia was nearly as large as that in normoxia. Therefore assuming the same amplitude of $Pc'_{O_2}$ fluctuation in normoxia and moderate hypoxia, we tried to elucidate the influence of the slope of the $O_2$ dissociation curve and of venous admixture on the transmission of $Pc'_{O_2}$ fluctuation to the arterial side.

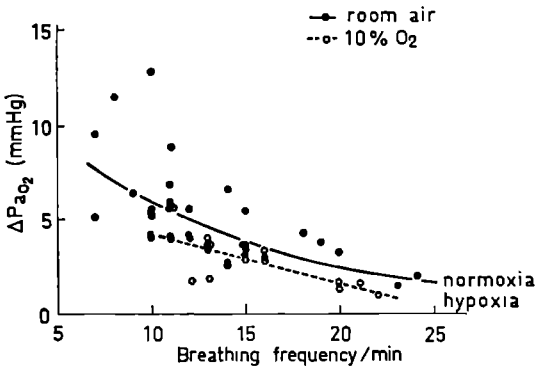



Fig. 2. Relationship between the amplitude of respiratory fluctuation of $Pa_{O_2}$ ($\triangle Pa_{O_2}$) and breathing frequency in dogs breathing room air or 10% $O_2$ in $N_2$ spontaneously. Solid and broken lines are regression lines for normoxia and hypoxia, respectively.

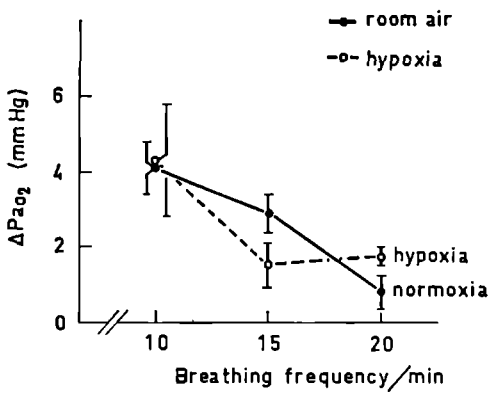



Fig. 3. Same relationship as in figure 2 in dogs ventilated artificially. Total ventilation was maintained constant while ventilatory frequency was changed. Vertical bars show $\pm$ one standard error.

Figure 4 shows the $O_2$ dissociation curve given by Rossing and Cain (1966) for dogs at 38°C and pH 7.4. For the mean, the highest and the lowest fluctuation of $Pc'_{O_2}$, the shunt ratio, and $P\bar{v}_{O_2}$, the following values were assumed for normoxia: 110 mm Hg, 115 mm Hg, 105 mm Hg, 0.05, and 40 mm Hg, and for hypoxia: 50 mm

Hg, 55 mm Hg, 45 mm Hg, 0.05, and 30 mm Hg, respectively. The corresponding arterial points of the fluctuating $P_{O_2}$ were obtained from saturation:

$$Sa_{O_2} = Sc'_{O_2}\,(1 - Qs/Qt) + S\bar{v}_{O_2} \cdot Qs/Qt$$

where Qs/Qt is the shunt ratio. The influence of dissolved $O_2$ was neglected. $S\bar{v}_{O_2}$ was obtained from $P\bar{v}_{O_2}$ on the $O_2$ dissociation curve at pH 7.35. The amplitude of $Pa_{O_2}$ fluctuation was for normoxia and for hypoxia 5.3 mm Hg and 9.4 mm Hg, respectively, both corresponding to that of 10 mm Hg in $Pc'_{O_2}$. Thus the attenuation of respiratory fluctuation of $P_{O_2}$ in blood is less in moderate hypoxia than in normoxia; even by assuming much lower $P\bar{v}_{O_2}$ in hypoxia resulting in a larger effect of venous admixture, the amplitude of $Pa_{O_2}$ fluctuation in hypoxia still remains larger than in normoxia. Furthermore when hypoxia becomes severe and venous admixture is considered to occur in the steepest part of the $O_2$ dissociation curve, the attenuation of the amplitude of respiratory $P_{O_2}$ fluctuation would be absent or even an enhancement might result. Hence the steeper slope of the $O_2$ dissociation curve in the hypoxic range does not tend to diminish the amplitude of $Pc'_{O_2}$ fluctuation any more than in normoxia through venous admixture.

Therefore the smaller amplitude of $Pa_{O_2}$ fluctuation in hypoxia when compared

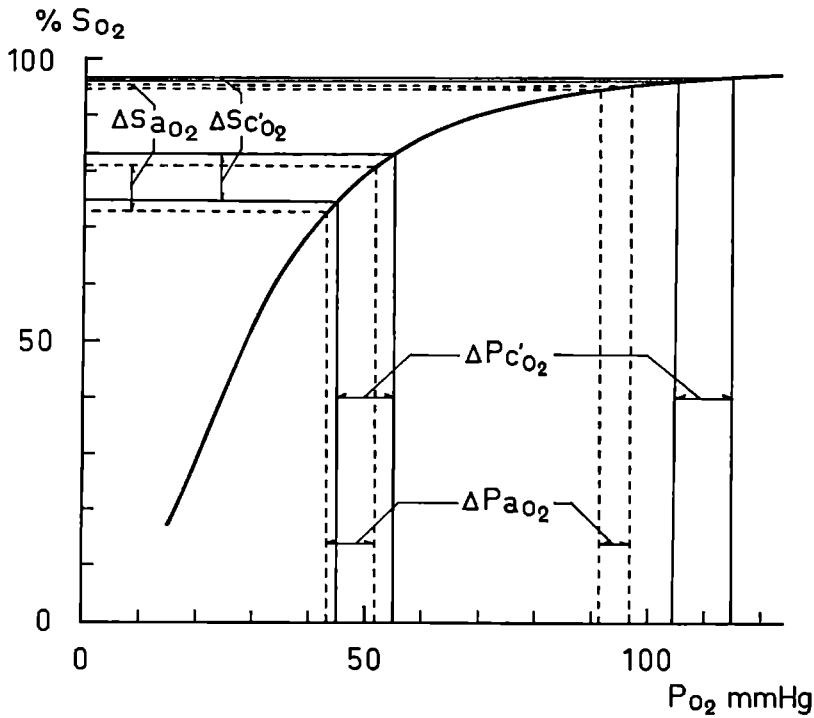



Fig. 4. Influence of venous admixture on the amplitude of respiratory $O_2$ fluctuation during transport from endcapillary to aortic blood in normoxia and in moderate hypoxia. $\Delta\, Sa_{O_2}$, $\Delta\, Sc'_{O_2}$, $\Delta\, Pa_{O_2}$, and $\Delta\, Pc'_{O_2}$ are amplitudes of $O_2$ fluctuation in saturation and $O_2$ pressure in arterial and endcapillary blood, respectively. For details see text.

with normoxia as obsereved by us or Purves (1966) should be attributed to the difference in the amplitude of $Pc'_{O_2}$ between hypoxia and normoxia, i.e., to the smaller amplitude of $Pc'_{O_2}$ in hypoxia. This assertion is not at all contradictory to the results of Flumerfelt and Crandall (1968) and Hlastala (1972) since these authors worked on the basis of a single alveolar lung model. In the lung model with two alveolar compartments or in the real lung, however, it is likely that the amplitude of respiratory fluctuations of $P_{A_{O_2}}$ changes in hypoxia due to the change of $\alpha$, the index of ventilation-perfusion ratio. It is well known since Euler and Liljestrand (1946) that pulmonary arterial pressure (perfusion ressure) increases during hypoxia. Fowler and Read (1963) observed that the upper zones of the lung were perfused by a considerably greater proportion of pulmonary blood flow in hypoxic man, and the influence of increased pulmonary arterial pressure on the arterial-alveolar $P_{CO_2}$ difference was shown by Askrog (1966). Therefore $\alpha$ is possibly increased as a result of improved perfusion and consequently the amplitude of respiratory $P_{A_{O_2}}$ fluctuation might be diminished. However, we could not find any significant decrease of arterial-alveolar $P_{CO_2}$ difference in the hypoxic dog (Fukuma *et al.*, 1970). At this moment it is therefore not clear as to how far a possible change of $\alpha$ in hypoxia would play a role in changing the amplitude of $P_{A_{O_2}}$ fluctuation.

On the other hand the changes in circulatory condition in hypoxia would tend to reduce the attenuation of the amplitude of respiratory $P_{A_{O_2}}$ fluctuations during transmission to the arterial side by increase of the heart rate (figure 4, chapter 2) as shown by Lutz and Schneider (1919) and by numerous other workers (Grollman, 1930; Asmussen and Chiodi, 1941; Dripps and Comroe, 1947; Albers and Usinger, 1956; Carrell and Milhorns, 1971), and by shortening the lung circulation time (Bierman, 1951). Thus, if there is some decrease in the amplitude of $P_{A_{O_2}}$ fluctuation in hypoxia due to a change of $\alpha$, the reduction of the amplitude of $Pa_{O_2}$ fluctuation might be less than expected from the change on the alveolar side due to a compensatory change in the circulatory condition.

The increase of the amplitude of respiratory fluctuation of $Pa_{O_2}$ during hyperoxygenation could be explained from the shape of the $O_2$ dissociation curve which is practically straight in the hyperoxic range. Therefore, as far as venous admixture is not as large as to reduce $Pa_{O_2}$ to the curved portion of the $O_2$ dissociation curve, the amplitude of respiratory $Pa_{O_2}$ fluctuation will be influenced by circulatory factors only. When 100 % $O_2$ is administered, there exist only $O_2$ and $CO_2$ in the alveolar gas. In consequence there would be no cyclical change in R, as shown by several investigators (references in chapter 1), in the alveolar gas during the respiratory cycle as long as total alveolar pressure is atmospheric. Considering that $Pc'_{O_2}$ is in equilibrium with $P_{A_{O_2}}$ and that the total pressure is atmospheric, the amplitude of $Pc'_{O_2}$ must be the same as that of $Pc'_{CO_2}$. Hence the amplitude of $\Delta Pa_{O_2}$ would also be equal to that of $\Delta Pa_{CO_2}$ though the direction of the fluctuation is reversed. Unfortunately it is not easy to correctly measure the amplitude of $Pa_{O_2}$ fluctuation in 100 % $O_2$ breathing due to bradycardia and arrhythmia which cause an increase of the pulsatile fluctuation of $Pa_{O_2}$ with the heart beat.

We adopted the gamma variate for the transfer function as reported by Thompson *et al.* (1964) in calculating the reduction ratio of the amplitude of $P_{AO_2}$ or $Pc'_{O_2}$ between lung and aorta. Several other transfer functions were reported by Newman *et al.* (1951), Conrad *et al.* (1965), Bassingthweighte *et al.* (1966), Lange *et al.* (1966), and Schlossmacher *et al.* (1967). Recently Harris and Newman (1970) reviewed and compared these different transfer functions. For all these transfer functions there was good agreement between theoretical and experimental curves; we have chosen the gamma variate since it was the most convenient for our purpose.

It might be imagined that the measurement of $Pa_{O_2}$ in the left atrium or the pulmonary vein would be more suited for a comparison of the patterns of $P_{AO_2}$ and $Pa_{O_2}$ fluctuations because the influence of the mixing effect in the left ventricle could thus be avoided. In practice, however, it was quite difficult to obtain stable $P_{O_2}$ records in the left atrium or in the pulmonary vein because of contact of the $P_{O_2}$ electrode tip with the heart or vessel wall. Furthermore any pulmonary vein would not be suited for measurement of $Pa_{O_2}$ because it represents only one region of the lung, at best one lobe, whereas the calculated $P_{AO_2}$ holds for the whole lung.

Small fluctuations on the in vivo $P_{O_2}$ record with the same frequency as the heart beat were always observed in our experiments. Two explanations are offered for the origin of these pulsatile fluctuations in the $P_{O_2}$ record: a physiological phenomenon according to Purves (1966) or an artefact as suggested by Band *et al.* (1969a) for the same phenomenon concerning pH. It might be of interest to look for a possible explanation of these pulsatile fluctuations. In terms of arguments for a physiological phenomenon the following factors might be considered:

1. pulsatile nature of pulmonary capillary flow;
2. mixing with residual blood in the left ventricle;
3. possible pulsatile variation of venous admixture.

Pulsatile pulmonary capillary flow was shown to cause pulsatile variation of $P_{O_2}$ in alveolar gas and in endcapillary blood by Flumerfelt and Crandall (1968) and Hlastala (1972). Possible variation of contact time (= capillary blood volume/cardiac output) due to pulsatile capillary flow would also cause pulsatile variation of $Pc'_{O_2}$ if the contact time were not long enough for equilibration with alveolar gas. The endcapillary blood proceeds through the pulmonary venous side from various parts of the lung to the left atrium with an appearance time of about 1 sec and a mean circulatoin time of 2 sec. On arrival at the left atrium, blood from various parts of the lung with pulsatile $P_{O_2}$ variations will be mixed with some time lag corresponding to the difference of circulation time for the different parts of the lung. It is hardly imaginable, in such a condition, that the pulsatile variations of $P_{O_2}$ could still persist in a regular pattern with the heart beat in the left atrium, let alone in the aorta after passing the mixing chamber of the left ventricle. Partial mixing with residual blood in the left ventricle was mentioned by Purves (1966) as an explanation for the pulsatile fluctuation on his $P_{O_2}$ record. If this is the case, the fluctuation of $P_{O_2}$ with the heart beat should have the characteristic pattern of a ventricular wash-out curve, as shown by numerous investigators (Holt, 1956 and 1966; Swan and Beck, 1960; Bristow *et al.*,

1963; Rapaport, 1965 and 1966), i.e., it should be step-like, and its amplitude should be determined by the $P_{O_2}$ difference between inflow and residual blood and $Q_{cs}/Q_{ed}$, but not dependent on the mean $Pa_{O_2}$, i.e., it should be almost indifferent to the oxygenation level. The third factor, a possible pulsatile variation of venous admixture, includes coronary venous drainage into the left chamber and other physiological and anatomical shunt components. However, as far as this venous admixture occurs before or in the left heart chamber, it must pass the mixing chamber before it appears in the aorta; therefore it would also follow the pattern of indicator dilution in the ventricle.

We observed the following characteristics of the pulsatile fluctuation of $P_{O_2}$:

1. each fluctuation had a rather sharp peak instead of a step-like pattern;
2. its amplitude was closely related to mean $Pa_{O_2}$;
3. in the left atrium there was a similar fluctuation on the $P_{O_2}$ record;
4. when blood flow or pressure was measured in the neighborhood of the $P_{O_2}$ electrode, there was always a definite time relationship between pulsatile fluctuation of $P_{O_2}$ and pulsatile flow or pressure variation;
5. there was a similar pulsatile variation of $P_{O_2}$ in an in vitro roller pump system.

All these findings are contradictory to the above-mentioned arguments for a physiological phenomenon; therefore we conclude that the pulsatile fluctuation might be an artefact. This pulsatile fluctuation of $P_{O_2}$, however, does not influence the pattern of the respiratory variation of $Pa_{O_2}$ because the respiratory $Pa_{O_2}$ variation is separable from pressure or flow variation by changing the place of the $Pa_{O_2}$ measurement in the aorta, and is not deformed by it throughout the aorta (figure 6, chapter 2).

The oxygenation of arterial blood depends on the oxygenation level of $P\bar{v}_{O_2}$, inspiratory oxygen concentration, blood flow, alveolar ventilation, and distribution of ventilation-perfusion ratio in the lung. In the lung model used for the calculation of the moment-to-moment variation of $P_{AO_2}$, blood flow was presumed to change cyclically, by some authors, in addition to tidal ventilation. However, as shown here, $P\bar{v}_{O_2}$ may change cyclically with respiration. Consequently the flow pattern alone is not enough for the determination of gas exchange but the change of $P\bar{v}_{O_2}$ should also be considered. In practice it is not easy to combine flow and $P\bar{v}_{O_2}$ variations at the entrance to the lung capillaries since the pattern of $P\bar{v}_{O_2}$ at the entrance to the capillaries is unknown, and flow and $P\bar{v}_{O_2}$ will be transfered by different mechanisms, i.e., transmission of volume and transport of particles, respectively. Such a dissociation of flow transmission and $P\bar{v}_{O_2}$ transfer may be seen in figures 2 and 5 in chapter III where the peak of $P_{O_2}$ in the IVC is seen in the preinspiratory period and the trough around endinspiration (figure 2), whereas the peak of $P_{O_2}$ in the main pulmonary artery corresponds to endinspiration (figure 5) where pulmonary flow is maximum (references, chapter I).

The origin of the respiratory variation of $P\bar{v}_{O_2}$ could be attributed mainly to the fluctuation of $Pv_{O_2}$ in the IVC (where it is much larger than in the SVC) resulting from the phasic variation of the outflow from various organs. It is well known that venous oxygenation is different from organ to organ and therefore Zuntz and Hagemann (1898) had to sample venous blood from the neighborhood of the right

atrium to apply Fick's principle to the measurement of cardiac output. For example, arterio-venous $O_2$ difference is in the coronary circulation 10–13 vol. % (Bing, 1951; Leight *et al.*, 1956; Maxwell *et al.*, 1959; Yurchak *et al.*, 1964), in the hepatic circulation 6.4–9.2 vol. % (Blaloch and Mason, 1936; Selkurt and Brecher, 1956), in the cerebral circulation 5–7 vol. % (Kety, 1956; Gibbs *et al.*, 1942; Sokoloff, 1960), and in renal circulation 1.6 vol. % for man and 3.0 vol. % for the dog (Selkurt, 1963).

Respiratory variation of venous return was noticed already by Valsalva (1723; quoted by Franklin, 1937) in the jugular vein of a dog, but the exact nature of caval venous return in connection with respiratory movement was established only by Mixter (1953) and Brecher and Mixter (1953). Concerning the outflow pattern from abdominal organs there still was no agreement. A recent study by Moreno *et al.* (1967) seemed to have given an answer concerning the behavior of hepatic outflow with respiration, i.e., hepatic outflow diminished during inspiration. However, their conclusion is contradicted by our findings concerning the $P_{O_2}$ variation in the thoracic IVC in supine dogs; we concluded that the lowering of $P_{O_2}$ in the thoracic IVC during inspiration was due to the increase of hepatic contribution to the IVC (chapter III). This conclusion was substantiated in supine dogs (chapter IV) by showing that hepatic outflow increased during inspiration and that this increase was responsible for the increase of venous return in the thoracic IVC during inspiration since abdominal caval flow below the liver decreased during the same period. It is interesting to recall the conclusion of Gollwitzer-Meier (1932) that 'In der oberen Hohlvene und in den Lebervenen wird der venöse Rückfluss während der Einatmung begünstigt, während der Ausatmung verschlechtert; in der unteren Hohlvene und im Pfortadergebiet hemmt die Ausatmung den Rückfluss, die Einatmung begünstigt ihn.' It must be kept in mind, however, that this discussion only holds for dogs in supine position. In dogs positioned laterally hepatic outflow may decrease during inspiration as pointed out by Moreno *et al.* (1967) and by other authors (references, chapter 3 and 4).

Nowadays it is generally accepted that the collapse theory of Holt (1941, 1943, 1944, 1959) and of the group of Duomarco (1954, 1963) presents one of the most important factors regulating venous flow, as established by Brecher (1956) for superior vena cava flow. For the IVC Norhagen (1963) showed narrowing of the segment between the diaphragm and the lower surface of the liver during inspiration and Doppman *et al.* (1966) demonstrated collapse of the infradiaphragmatic portion with increase of intra-abdominal pressure. The collapse of the caval segment between diaphragm and lower surface of the liver might explain the decrease of abdominal caval flow during inspiration in supine and in lateral position. Since hepatic outflow increases during inspiration, the collapse of IVC during inspiration cannot involve the hepatic venous junction to the IVC in supine position. Hepatic outflow decreases during inspiration in lateral or in prone position with increase of caval pressure difference between thoracic and abdominal cavities. There might be two ways to explain the decrease of hepatic outflow with inspiration:

1. collapse involving the hepatic venous junction to the IVC;
2. collapse of the hepatic veins themselves.

The latter was stressed by Brauer (1963) to explain the decrease of hepatic venous return during inspiration: 'Since the conduits (or important segments thereof) are collapsible, and since the surrounding liver tissue is not very rigid, the whole behaves much like a collapsible conduit suspended in a fluid phase. Pressure increase in the stationary fluid phase will collapse the conduit at its low pressure, downstream end first, displacing the blood out upstream if the extravascular pressures are large enough.' When considering that the hepatic veins open to the IVC just below the diaphragm (Norhagen, 1963), the involvement of hepatic venous junction in the collapse should occur in a later stage of the collapse. In this study we could not decide which was the most probable explanation; but since a collapse of the hepatic veins was demonstrated with cineangiography by Brauer *et al.* (1960), Moreno (1964), and Moreno *et al.* (1967), the second explanation seems to be more likely. However, we should keep in mind that the experimental conditions of these authors might not be the same as ours; therefore their findings may not provide direct evidence in favor of our explanation.

As far as $Pv_{O_2}$ was measured in the thoracic vena cava adjacent to the right atrium, possible formation of discrete blood lamellae in the vena cava due to the confluence of blood from different organs with different $P_{O_2}$, as observed by Franklin (1937), should not influence the $P_{O_2}$ pattern as measured by the $P_{O_2}$ electrode since the electrode is shifted from lamella to lamella during the recording as mentioned in chapter III. Such a lamellae formation of the blood stream, however, might affect the measurement of $P_{O_2}$ pattern in the abdominal vena cava where this kind of electrode displacement with every heart beat was not seen. We observed during laparotomy that the brightness of the caval blood changed periodically with respiration cranially to the confluence of the renal veins. The renal veins supply half or even more of the abdominal caval flow below the liver (figures 2 to 6 in chapter 4; Attinger *et al.*, 1967; Dedichen and Schenk, 1971). But when considering the rather consistent variation of IVC flow with respiratory movement below the renal veins, the shift of the $P_{O_2}$ electrode from lamella to lamella should not be the only reason for the respiratory variation of $P_{O_2}$ in the abdominal vena cava since the electrode still is located randomly within the vessel during various experiments.

## References

Albers, C. and W. Usinger (1956). Der Kreislauf des Hundes bei akutem Sauerstoffmangel. *Pflügers Arch.* 263: 201–226.

Altshuler, B., E. D. Palmes, L. Yarmus and N. Nelson (1959). Intrapulmonary mixing of gases studied with aerosols. *J. Appl. Physiol.* 14: 321–327.

Askrog, V. (1966). Changes in $(a\text{-}A)CO_2$ difference and pulmonary artery pressure in anesthetized man. *J. Appl. Physiol.* 21: 1299–1305.

Asmussen, E. and H. Chiodi (1941). The effect of hypoxia on ventilation and circulation in man. *Am. J. Physiol.* 132: 426–436.

Åström, A. (1952). On the action of combined carbon dioxide excess and oxygen deficiency in the regulation of breathing. *Acta Physiol. Scand. 27, Suppl.* 98: 1–61.

Attinger, E. O., H. Sugawara, A. Navarro, T. Mikami and R. Martin (1967). Flowpatterns in the peripheral circulation of the anesthetized dog. *Angiologica* 4: 1–27.

Band, D. M., I. R. Cameron and S. J. G. Semple (1969a). Oscillations in arterial pH with breathing in the cat. *J. Appl. Physiol.* 26: 261–267.

Band, D. M., I. R. Cameron and S. J. G. Semple (1969b). Effect of different methods of $CO_2$ administration on oscillations of arterial pH in the cat. *J. Appl. Physiol.* 26: 268–273.

Bassingthweighte, J. B., F. H. Ackerman and E. H. Wood (1966). Applications of the lagged normal density curves as a model for arterial dilution curves. *Circulation Res.* 18: 398–415.

Bergman, N. A. (1961). Cyclic variations in blood oxygenation with the respiratory cycle. *Anesthesiology* 22: 900–908.

Bergman, N. A. (1963). Effect of different breathing patterns on alveolar-arterial gradients in dogs. *J. Appl. Physiol.* 18: 1049–1052.

Bergman, N. A. (1967). Effects of varying respiratory waveforms on gas exchange. *Anesthesiology* 28: 390–395.

Bierman, H. R. (1951). Pulmonary circulation times with particular relationship to acute hypoxia. *Am. J. med. Sci.* 222: 162–173.

Bing, R. J. (1951). The coronary circulation in health and disease as studied by coronary sinus catheterization. *Bull. New York Acad. Med.* 27: 407–424.

Birath, G. (1959). Respiratory dead space measurements in a model lung and healthy human subjects according to the single breath method. *J. Appl. Physiol.* 14: 517–520.

Bjurstedt, A. G. H. (1946). Interaction of centrogenic and chemoreflex control of breathing during oxygen deficiency. *Acta Physiol. Scand. 12, Suppl.* 38: 1–88.

Blalock, A. and M. F. Mason (1936). Observations on the blood flow and gaseous metabolism of the liver of unanesthetized dogs. *Am. J. Physiol.* 117: 328–334.

Bosman, A. R., A. J. Honour, G. De J. Lee, R. Marshall and F. D. Stott (1964). A method for measuring instantaneous pulmonary capillary bloodflow and right ventricular stroke volume in man. *Clin. Sci.* 26: 247–260.

Bosman, A. R., G. De J. Lee and R. Marshall (1965). The effect of pulsatile capillary blood flow upon gas exchange within the lung of man. *Clin. Sci.* 28: 295–309.

Brauer, R. W., R. F. McElroy, Jr. and G. F. Leong (1960). Blood flow in the hepatic veins of the rat. *Physiologist* 3(3): 28.

Brauer, R. W. (1963). Liver circulation and function. *Physiol. Rev.* 43: 115–213.

Brecher, G. A. and G. Mixter, Jr. (1953). Effect of respiratory movements on superior cava flow under normal and abnormal conditions. *Am. J. Physiol.* 172: 457–461.

Brecher, G. A. (1956). Venous Return. New York, Grune & Stratton.

Bristow, J. D., R. E. Ferguson, F. Mintz and E. Rapaport (1963). Thermodilution studies of ventricular volume changes due to isoproterenol and bleeding. *J. Appl. Physiol.* 18: 129–133.

Carrell, D. E. and H. T. Milhorn, Jr. (1971). Dynamic respiratory and circulatory responses to hypoxia in the anesthetized dogs. *J. Appl. Physiol.* 30: 305–312.

Chilton, A. B. and R. W. Stacy (1952). A mathematical analysis of carbon dioxide respiration in man. *Bull. Math. Biophys.* 14: 1–18.

Chilton, A. B., D. S. Barth and R. W. Stacy (1954). A mathematical analysis of oxygen respiration in man. *Bull. Math. Biophys.* 16: 1–14.

Conrad, W. A., R. W. Broncato and C. A. Pallini (1965). Indicator dilution considered as the delayed pulse responses on an overdamped resonant circuit. *J. Appl. Phys.* 36: 861–863.

Cumming, G., J. Crank, K. Horsfield and I. Parker (1966). Gaseous diffusion in the airways of the human lung. *Respir. Physiol.* 1: 58–74.

Cumming, G., K. Horsfield, J. G. Jones and D. C. F. Muir (1967). The influence of gaseous diffusion on the alveolar plateau at different lung volumes. *Respir. Physiol.* 2: 386–398.

Cumming, G., K. Horsfield and S. B. Preston (1971). Diffusion equilibrium in the lungs examined by nodal analysis. *Respir. Physiol.* 12: 329–345.

Dedichen, H. and W. G. Schenk, Jr. (1971). Cardiac output and its regional distribution in the dog. *J. Thorac. Cardiovasc. Surg.* 61: 110–120.

Doppman, J., R. M. Rubinson, S. D. Rockoff, J. S. Vasko, R. Shapiro, and A. G. Morrow (1966). Mechanism of obstruction of the infradiaphragmatic portion of the inferior vena cava in the presence of increased intra-abdominal pressure. *Invest. Radiol.* 1: 37–53.

Dripps, R. D. and J. H. Comroe, Jr. (1947). The effect of the inhalation of high and low oxygen concentrations on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation (oximeter) of normal individuals. *Am. J. Physiol.* 149: 277–291.

DuBois, A. B., A. G. Britt and W. O. Fenn (1952). Alveolar $CO_2$ during the respiratory cycle. *J. Appl. Physiol.* 4: 535–548.

DuBois, A. B. and R. Marshall (1957). Measurements of pulmonary capillary blood flow and gas exchange throughout the respiratory cycle in man. *J. Clin. Invest.* 36: 1566–1571.

Duomarco, J. L. and R. Rimini (1954). Energy and hydraulic gradients along systemic veins. *Am. J. Physiol.* 178: 215–220.

Duomarco, J. L., R. Rimini, C. E. Giambruno, R. Seoane and M. Haendel (1963). Systemic venous collapse in man. *Am. J. Cardiol.* 11: 357–361.

Euler, U. S. v. and G. Liljestrand (1946). Observations on the pulmonary arterial blood pressure in the cat. *Acta Physiol. Scand.* 12: 301–320.

Flumerfelt, R. W. and E. D. Crandall (1968). An analysis of external respiration in man. *Math. Biosci.* 3: 191–204.

Fowler, W. S. (1948). Lung function studies. II. The respiratory dead space. *Am. J. Physiol.* 154: 405–416.

Fowler, K. T. and J. Read (1963). Effect of alveolar hypoxia on zonal distribution of pulmonary blood flow. *J. Appl. Physiol.* 18: 244–250.

Franklin, K. J. (1937). A Monograph on Veins. Springfield, Illinois, Charles C Thomas.

Frumin, M. J., N. A. Bergman, D. A. Holaday, H. Rackow and E. Salanitre (1959). Alveolar-arterial $O_2$ differences during artificial respiration in man. *J. Appl. Physiol.* 14: 694–700.

Fukuma, S., F. N. Wildeboer-Venema, S. Horie, H. Yokota, Y. Honda, J. H. Schuurmans Stekhoven and F. Kreuzer (1970). Pulmonary diffusing capacity in the dog as influenced by anesthesia and ventilatory regime. *Respir. Physiol.* 8: 311–331.

Georg, J., N. A. Lassen, K. Mellemgaard and A. Vinther (1965). Diffusion in the gas phase of the lungs in normal and emphysematous subjects. *Clin. Sci.* 29: 525–532.

Gibbs, E. L., W. G. Lennox, L. F. Nims and F. A. Gibbs (1942). Arterial and cerebral venous blood; arterial-venous difference in man. *J. Biol. Chem.* 144: 325–332.

Gollwitzer-Meier, Kl. (1932). Venensystem und Kreislaufregulierung. *Ergebn. Physiol.* 34: 1145–1255

Grollman, A. (1930). Physiological variations of the cardiac output of man. VII. The effect of high altitude on the cardiac output and its related functions: An account of experiments conducted on the summit of Pike's Peak, Colorado. *Am. J. Physiol.* 93: 19–39.

Haldane, J. S. and J. G. Priestley (1905). The regulation of lung ventilation. *J. Physiol.* (Londen) 32: 225–266.

Harris, T. R. and E. V. Newman (1970). An analysis of mathematical models of circulatory indicator-dilution curves. *J. Appl. Physiol.* 28: 840–850.

Hlastala, M. P. (1972). A model of fluctuating alveolar gas exchange during the respiratory cycle. *Respir. Physiol.* 15: 214–232.

Holt, J. P. (1941). The collapse factor in the measurement of venous pressure. *Am. J. Physiol.* 134: 292–299.

Holt, J. P. (1943). The effect of positive and negative intra-thoracic pressure on peripheral venous pressure in man. *Am. J. Physiol.* 139: 208–211.

Holt, J. P. (1944). The effect of positive and negative intrathoracic pressure on cardiac output and venous pressure in the dog. *Am. J. Physiol.* 142: 594–603.

Holt, J. P. (1956). Estimation of the residual volume of the ventricle of the dog's heart by two indicator dilution technics. *Circulation Res.* 4: 187–195.

Holt, J. P. (1959). Flow of liquids through "collapsible" tubes. *Circulation Res.* 7: 342–353.

Holt, J. P. (1966). Indicator-dilution methods: Indicators, injection, sampling and mixing problems in measurement of ventricular volume. *Am. J. Cardiol.* 18: 208–225.

Honda, Y. and M. Ueda (1961). Fluctuations of arterial pH associated with the respiratory cycle in dogs. *Jap. J. Physiol.* 11: 223–228.

Kaplan, A. S. and P. Kimbal (1970). Pulmonary blood flow waves in subjects with abnormal pulmonary hemodynamics. 28: 793–801.

Karatzas, N. B. and G. De J. Lee (1969). Propagation of blood flow pulse in the normal human pulmonary arterial system. *Circulation Res.* 25: 11–21.

Karatzas, N. B. and G. De J. Lee (1970). Instantaneous lung capillary blood flow in patients with heart disease. *Cardiovascular Res.* 4: 265–273.

Kety, S. S. (1956). Human cerebral blood flow and oxygen consumption as related to aging. *J. Chron. Dis.* 3: 478–486.

Kimmich, H. P. and F. Kreuzer (1969). Catheter $P_{O_2}$ electrode with low flow dependency and fast response. In: Oxygen Pressure Recording in Gases, Fluids and Tissues, edited by F. Kreuzer. Progr. in Resp. Res. Vol. 3, edited by H. Herzog. Basel, Karger, pp. 100–110.

Krogh, A. and J. Lindhard (1913). The volume of the "dead space" in breathing. *J. Physiol.* (Londen) 47: 30–43.

Krogh, A. and J. Lindhard (1914). On the average composition of the alveolar air and its variations during the respiratory cycle. *J. Physiol.* (Londen). 47: 431–445.

Krogh, A. and J. Lindhard (1917). The volume of the dead space in breathing and the mixing of gases in the lungs of man. *J. Physiol.* (Londen) 51: 59–90.

La Force, R. C. and B. M. Lewis (1970). Diffusional transport in the human lung. *J. Appl. Physiol.* 28: 291–298.

Lamb, T. W., N. R. Anthonisen and S. M. Tenney (1965). Controlled frequency breathing during muscular exercise. *J. Appl. Physiol.* 20: 244–248.

Lange, R. L., J. D. Horgan, J. T. Botticelli, T. Tsagaris, R. P. Carlisle and H. Kuida (1966). Pulmonary to arterial circulatory transfer function: importance in respiratory control. *J. Appl. Physiol.* 21: 1281–1291.

Lee, G. De J. and A. B. DuBois (1955). Pulmonary capillary blood flow in man. *J. Clin. Invest.* 34: 1380–1390.

Leight, D., V. De Fazio, F. N. Talmers, T. J. Regan and H. K. Hellems (1956). Coronary blood flow, myocardial oxygen consumption and myocardial metabolism in normal and hyperthyroid human subjects. *Circulation.* 14: 90–99.

Lilienthal, J. L., Jr., R. L. Riley, D. D. Proemmel and R. E. Franke (1946). An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. *Am. J. Physiol.* 147: 199–216.

Linderholm, H., P. Kimbal, D. H. Lewis and A. B. DuBois (1962). Pulmonary capillary blood flow during cardiac catheterization. *J. Appl. Physiol.* 17: 135–141.

Lutz, B. R. and E. C. Schneider (1919). Circulatory response to low oxygen tensions. *Am J. Physiol.* 50: 228–251.

Maxwell, G. M., C. W. Crumpton, G. G. Rowe, D. H. White and C. A. Castillo (1959). The effects of theophylline ethylenediamine (Aminophyline) on the coronary hemodynamics of normal and diseased hearts. *J. Lab. and Clin. Med.* 54: 88–95.

Mixter, G., Jr. (1953). Respiratory augmentation of inferior vena caval flow demonstrated by a low-resistance phasic flowmeter. *Am. J. Physiol.* 172: 446–456.

Moreno, A. H. (1964). Perpetuation of cirrhotic ascites as a result of altered regulation of venous return. *Bull. New York Acad. Med.* 40: 80.

Moreno, A. H., A. R. Burchell, R. van der Woude and J. H. Burke (1967). Respiratory regulation of splanchnic and sytemic venous return. *Am. J. Physiol.* 213: 455–465.

Muir, D. C. F. (1967). Distribution of aerosol particles in exhaled air. *J. Appl. Physiol.* 23: 210–214.

Namur, M., J. M. Petit, D. Lagneaux and R. Sneppe (1961). Variations de la saturation artérielle en

$O_2$ au cours du cycle respiratoire. *Arch. Int. Physiol. Biochim.* 69: 731–736.

Newman, E. V., M. Marrell, A. Genecin, C. Monge, W. R. Milonso and W. P. McKeevers (1951). The dye dilution method for describing the central circulation. *Circulation* 4: 735–746.

Nims, L. S. and C. Marshall (1938). Blood pH in vivo. I. Changes due to respiration. *Yale J. Biol. and Med.* 10: 445–448.

Norhagen, Å. (1963). Selective angiography of the hepatic veins. *Acta Radiol. Suppl.* 221: 1–121.

Nye, R. E. (1970). Influence of the cyclical pattern of ventilatory flow on pulmonary gas exchange. *Respir. Physiol.* 10: 321–337.

Otis, A. B. (1964). Quantitative relationships in steady-state gas exchange. In: Handbook of Physiology, Sec. 3, Respiration, Vol. I, edited by W. O. Fenn and H. Rahn, Washington, D. C., American Physiological Society, pp. 681–698.

Power, G. G. (1969). Gaseous diffusion between airways and alveoli in the human lung. *J. Appl. Physiol.* 27: 701–709.

Purves, M. J. (1966). Fluctuations of arterial oxygen tension which have the same period as respiration *Respir. Physiol.* 1: 249–344.

Rapaport, E., M. Wong, R. E. Fergson, P. Bernstein and B. D. Wiegand (1965). Right ventricular volumes in patients with and without heart failure. *Circulation* 31: 531–541.

Rapaport, E. (1966). Usefulness and limitations of thermal washout technics in ventricular volume measurement. *Am. J. Cardiol.* 18: 226–234.

Rauwerda, P. E. (1946). Unequal ventilation of different parts of the lung and the determination of cardiac output. Thesis. University of Groningen.

Rossing, R. G. and S. M. Cain (1966). A nomogram relating $P_{O_2}$, pH, temperature, and hemoglobin saturation in the dog. *J. Appl. Physiol.* 21: 195–201.

Saidel, G. M., T. C. Militano and E. H. Chester (1971). Pulmonary gas transport characterization by a dynamic model. *Respir. Physiol.* 12: 305–328.

Schlossmacher, E. J., H. Weinstein, S. Lochaya and A. B. Shaffer (1967). Perfect mixers in series model for fitting venoarterial indicator-dilution curves. *J. Appl. Physiol.* 22: 327–332.

Selkurt, E. E. and G. A. Brecher (1956). Splanchnic hemodynamics and oxygen utilization during hemorrhagic shock in the dog. *Circulation Res.* 4: 693–704.

Selkurt, E. E. (1963). The renal circulation. In: Handbook of Physiology, Sec. 2, Circulation, Vol. II, edited by W. F. Hamilton and P. Dow, Washington, D. C., American Physiological Society, pp. 1457–1516.

Shepard, R. H., E. J. M. Campbell, H. B. Martin and T. Enns (1957). Factors affecting the pulmonary dead space as determined by single breath analysis. *J. Appl. Physiol.* 11: 241–244.

Sokoloff, L. (1960). Metabolism of the central nervous system in vivo. In: Handbook of Physiology, Sec. I, Neurophysiology, Vol. III, edited by J. Field, H. W. Magoun and V. E. Hall, Washington, D. C., American Physiological Society, pp. 1843–1864.

Suwa, K. and H. H. Bendixen (1972). Pulmonary gas exchange in a tidally ventilated single alveolus model. *J. Appl. Physiol.* 32: 834–841.

Swan, H. J. C. and W. Beck (1960). Ventricular nonmixing as a source of error in the estimation of ventricular volume by the indicator-dilution technic. *Circulation Res.* 8: 989–998.

Thompson, H. K., C. F. Starmer, R. E. Whalen and H. D. McIntosh (1964). Indicator transit time considered as a gamma variate. *Circulation Res.* 14: 502–515.

Vermeire, P. and J. Butler (1968). Effect of respiration on pulmonary capillary blood flow in man. *Circulation Res.* 22: 299–308.

Wasserman, K. and J. H. Comroe, Jr. (1962). A method for estimating instantaneous pulmonary capillary blood flow in man. *J. Clin. Invest.* 41: 401–410.

Wasserman, K., J. Butler and A. Van Kessel (1966). Factors affecting the pulmonary capillary blood flow pulse in man. *J. Appl. Physiol.* 21: 890–900.

Yamamoto, W. A. (1960). Mathematical analysis of the time course of alveolar $CO_2$. *J. Appl. Physiol.* 15: 215–219.

gedurende het transport. In de aorta treedt vrijwel geen daling op in de met de ademhaling samenhangende $P_{O2}$ schommelingen.

Het veneuze oxygenatieniveau is eveneens één van de belangrijkste componenten welke de gasuitwisseling in de long bepalen. In hoofdstuk III wordt hierop ingegaan. Bij honden onder narcose, liggend op de rug, wordt de veneuze $P_{O2}$ in de arteria pulmonalis, de vena cava superior en de vena cava inferior continu gemeten met behulp van de catheter $P_{O2}$-electrode. Een deel van de honden ademde spontaan, het andere deel werd kunstmatig geventileerd. De veneuze $P_{O2}$ vertoonde op alle meetplaatsen schommelingen met eenzelfde frequentie als de ademhaling. Deze fluctuaties waren in de vena cava inferior groter dan in de vena cava superior. Zij waren het grootst in de vena cava inferior juist vóór de inmonding in het atrium. De amplitudo van de fluctuerende $P_{O2}$ in de arteria pulmonalis is klein, en vertoont geen enkele correlatie met de ademfrequentie, noch met de absolute waarde van de $\bar{P}v_{O2}$, noch met het oxygenatieniveau.

Afsluiten van de venae renales door een tourniquet heeft tot gevolg dat de amplitudo in de vena cava inferior vlak vóór de inmonding in het rechter atrium lager wordt; afsluiten van de vena cava inferior onder de lever veroorzaakt demping, terwijl afsluiten onder de venae renales geen duidelijke verandering te zien geeft. Deze waarnemingen suggereren dat er een verschillend effect is, ten gevolge van de adembewegingen, op de veneuze flow uit diverse organen. De lever lijkt een verhoogde bijdrage te leveren aan de veneuze terugvloed in de vena cava inferior, gedurende inspiratie bij spontane ademhaling. Daarentegen schijnt het dat de nier géén duidelijke outflow veranderingen vertoont die in relatie met de adembewegingen staan.

De hypothetische conclusies betreffende de veneuze terugvloed, in hoofdstuk III, worden in hoofdstuk IV bewezen door meting van de veneuze terugstroom op 4 plaatsen in de vena cava, nl., craniaal en caudaal van de inmonding in het rechter atrium, en craniaal en caudaal ten opzichte van de venae renales. De lever- en nieroutflow werden berekend uit de flow in de vena cava inferior. De bloedstroom werd bepaald door de uitwendige diameter van de vena cava constant te houden, en de axiale bloedstroomsnelheid te meten met een electromagnetische stroomsnelheidsmeter.

In rugligging was er altijd een toename van de veneuze terugstroom in het thoracale gedeelte van de venae cavae en een toename van de lever-outflow gedurende inademing. De flow in het abdominale deel van de vena cava werd daarbij lager en vertoonde zelfs een relatie tot de ademhaling die tegengesteld was aan het thoracale patroon, en wel een dal tijdens inspiratie en een piek in het begin van expiratie. Als de hond op de zij of de buik lag, vertoonde de veneuze stroom in het thoracale deel van de vena cava inferior en uit de lever na een toename een geleidelijke daling, of zelfs een directe daling gedurende inspiratie. In de bloedstroom in de vena cava superior traden nauwelijks veranderingen op bij verandering van de lichaamshouding. In géén enkele houding toonde de outflow uit de nier een duidelijke relatie met de ademhaling.

Ten gevolge van een pneumoperitoneum met atmosferische druk was de toename

van de veneuze stroom in het thoracale deel van de vena cava inferior en uit de lever tijdens inspiratie lager bij de honden in rugligging.

De veranderingen in het patroon van de stroom in de vena cava en in de lever-outflow, ten gevolge van verschillende houdingen, worden verklaard uit een toename van de weerstand in de vena cava in het deel dat direct caudaal van het diafragma ligt, en/of een toename van de weerstand in de venae hepaticae. De weerstands-veranderingen worden geïnduceerd door een verandering van de lichaamshouding. Dit wordt weergegeven door de grootte van het preinspiratoire drukverschil in de vena cava, tussen thorax en abdomen. In zijligging bedraagt dit 5,3 $\pm$ 0,92 cm $H_2O$ (gemiddelde $\pm$ S.D., n = 14); in buikligging 6,5 $\pm$ 0,81 cm $H_2O$ (n = 4); en in rugligging 2,0 $\pm$ 0,85 cm $H_2O$ (n = 18). De verschillen ten opzichte van de druk in rugligging zijn statistisch significant ($p < 0{,}001$).

# STELLINGEN

## I

The common concept of alveolar ventilation does not imply the total gas volume which goes into and comes out of the alveolar space, but only part of it.

## II

The alveolar gas equation neglects reinspiration of dead space gas. However, in a steady-state lung model the result is the same whether or not reinspiration is considered.

## III

The respiratory fluctuation of arterial oxygen pressure will be attenuated in man more than observed in dogs.

## IV

The respiratory fluctuation of mixed venous oxygen pressure could be attributed mainly to the respiratory variation of hepatic outflow.

## V

The experimental condition has a profound influence on the results. Contradictory conclusions may be due to an apparently trifle difference in the experimental procedure.

## VI

No direct alveolar sample is really representative since any device introduced to collect regional samples mechanically distorts the normal ventilation-perfusion relationship.

H. Rahn and L. E. Farhi (1964). Handbook of Physiology, Section 3, Respiration, Vol. I, American Physiological Society, 735–766.

VII

After the introduction of $P_{CO_2}$ electrodes as accurate tool for evaluating $CO_2$ tension in the blood, the difficulty of assessing an artio-alveolar $CO_2$ pressure difference will not arise from inaccuracy of the blood value, but from lack of an alveolar $CO_2$ tension representing mean alveolar $CO_2$.

H. Rahn and L. E. Farhi (1964). Handbook of Physiology, Section 3, Pespiration, Vol. I, American Physiological Society, 735–766.

VIII

Ever since Haldane (1922), many investigators have argued that ventilation-perfusion ratio inequality affects the transfer of oxygen but not that of carbon dioxide. However, this is far from true.

J. B. West (1969). Respir. Physiol. 7: 88–110.

IX

The mean velocity in the vena cava is about 2/3 of that of the aorta (i.e., about 20 cm per sec in the resting state). This is a fairly high velocity and contradicts the naïve idea that the flow in veins is sluggish.

A. C. Burton (1966). Physiology and Biophysics of The Circulation. Year Book Medical Publishers, p. 66.

X

The choice of an appropriate compromise between the real situation and a theoretical model is one of the most important processes in the progress of knowledge.

XI

Hypotheses are instruments. It doesn't matter whether they are right or wrong as long as they stimulate thought.

Time, March 19, 1973, p. 43.

H. Yokota

Nijmegen, June 29, 1973